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THE PITUITARY ADAMANTINOMATA.

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INTRODUCTION.

THE pituitary adamantinoma may be defined as a variety of epithelial tumour, growing in the neighbourhood of the infundibulum, and originating in unobliterated portions of the fœtal craniopharyngeal duct; its minute structure is a duplicate of the embryonic enamel organ, and the general histological appearance resembles that of the adamantine tumours of the jaws. The derivation of the term is from the Greek ἀδάμας which was used of the hardness of stone, diamond, &c., i.e., something which cannot be worn away. The term adamantoblast was originally applied to the enamel-forming cell. Tumours arising from obliterated portions of the enamel organ are known as adamantinomata. The term adamantoblast has been discarded, however, in favour of the word ameloblast, but the designation adamantinoma has remained. The significance attached to the word as used in the sense of pituitary neoplasms does not refer to the consistency of tumours in that region, but their similarity in structure to the mandibular adamantinomata.

The histological classification of the heterotopic tumours of the

pituitary has always been a matter of very great difficulty, partly on account of their comparative rarity and partly because of the diversity of structure which they present. Although it has been fully appreciated that a large proportion of these growths are epithelial in nature, the fact that many of these epithelial structures conform in appearance to the fœtal enamel organ is not generally known. Onanoff [10], as long ago as 1892, pointed out this similarity, but the fact seems to have been lost sight of, and the existence of such tumours has been overlooked by every English writer on the subject.

Luschka [7], in 1860, was the first to describe collections of squamous epithelium adjacent to the normal hypophysis, but it was Erdheim who first suggested that such cells were remnants of the fœtal cranio-pharyngeal duct, and that the epithelial tumours of the infundibulum were actually duct tumours (Hypophysenganggeschwülste). Since that date, many records have appeared of epithelial tumours in this site, but in many instances the true nature of the neoplasm has been unrecognized.

Onanoff's original case was recorded in 1892, and the same case was also reported eight years later by Babinski [1].

Erdheim's paper [4] appeared in 1904, and in it he gave a very complete account of the clinical and pathological aspect of a series of seven hypophyseal duct tumours, and he pointed out that in three of these the structure recalled the histological picture of the adamantinomata.

Another case was reported in 1909 by Mackay and Bruce [2], but the resemblance to the enamel organ was never commented upon; their case was recorded as an "Epithelioma of the hypophyseal duct."

Two years later appeared communications from Strada [11], and from Farnell [5], each giving clinical and histological details of one case; in each instance, the nature of the neoplasm was recognized.

Teutschlaender's excellent paper [12] appeared in 1914, and contained a very full pathological discussion of one case. The tumour was designated as an infundibular cystic adamanto-carcinoma.

In 1916 appeared Warthin's paper [13] upon the chemistry of the fat in cases of pathological obesity; his first patient succumbed after an operation for the removal of a pituitary adamantinoma.

A detailed monograph on the hypophyseal duct tumours appeared in 1920, by Duffy [3]. In his paper he gives full clinical and pathological notes upon four such cases, in the second and third of which the tumours were adamantinomatous in nature. Duffy classified the duct tumours

into three types: (1) The papillary cysts; (2) the spinal-celled carcinomata, and (3) the adamantinomata.

The latest case mentioned in the literature was reported this year by Cornil [14].

In addition to these cases which we have quoted in which the adamantine structure of the growth was recognized by the author, or is recognizable from the description, there are doubtless many other reported cases which conform in appearance to the adamantinomata. Owing to the paucity of descriptive details or to the absence of photographic illustration, it is impossible to assume that any of such growths were of this nature though the probability is great.

This present paper aims at outlining the main clinical and pathological features of this group of tumours. In addition we are able to present seven cases of our own, four of which occurred in the practice of the National Hospital, Queen Square, one in that of St. Thomas's Hospital and one in that of University College Hospital.

Developmental Data.

From an embryological point of view the pituitary must be considered as a fusion of an upgrowth from the primitive stomodæum with a process of the fore-brain. Very early in fœtal life the ectoderm of the stomodæum becomes invaginated so as to form a recess; this pocket is Rathke's pouch. The ectoderm, which at an earlier period was in intimate contact with the epithelium of the fore-brain, now becomes more and more separated, especially in a caudad direction. Rathke's pouch thus becomes more deeply embedded; the proximal end narrows so as to form a hollow stalk, the canalis cranio-pharyngeus.

In gnathostomatous vertebrates this canal is gradually transformed into a solid rod of cells, which become more and more separated from the stomodæum by the formation of the sella turcica. Later it disappears altogether. It is possible to demonstrate occasionally in the human sphenoid a fine groove which indicates the tract of the primitive craniopharyngeal canal.

In the human fœtus the portion of the buccal invagination most distal to the stomodæum persists, and forms, in the 20-mm. embryo, a closed sac. Meanwhile an evagination has sprung from the floor of the fore-brain, immediately behind the optic recess, and forms the infundibular process. By the end of the fourth week Rathke's pouch and the infundibular process are in actual contact with each other.

The cells constituting the anterior aspect of Rathke's pouch now

proliferate with marked rapidity, so that in a twelve weeks' fœtus it is possible to distinguish definite cords of cells; by the fifteenth week the cords lie in clumps and show a tendency towards an acinar arrangement. In this manner the pars anterior of the pituitary gland is developed. At this stage the cells are entirely basophil in type. Connective tissue elements later grow in from the surrounding supporting structures, but acidophil cells do not appear until the ninth month of fœtal life. Meanwhile "the region of insertion of the erstwhile hypophyseal duct is carried upward, by the further rotation of the developing gland, to the anterior infundibular and upper pars anterior surfaces" (Duffy).

The posterior layer of Rathke's pouch develops into the pars intermedia of the pituitary gland. Two lateral outgrowths appear which fuse anteriorly and constitute the pars tuberalis. In the eighth-month fœtus the pars intermedia is visible as a highly vascular structure containing colloid.

The infundibular process of the fore-brain develops anteriorly into the pars posterior, whilst the hinder portion becomes the stalk or infundibulum. Along the anterior aspect of the infundibulum a thin layer of anterior lobe cells extends as far as the floor of the third ventricle.

Hence the portions of the mature pituitary which are of ectodermal origin are the pars anterior, the pars intermedia and the pars tuberalis; the cleft lying between the anterior and intermediate lobes represents the primitive cavity of Rathke's pouch.

In certain lower forms it is probable that the endoderm takes some part in the development of the pituitary by an infolding in the endoderm of the fore-gut, known as the pocket of Seessel. Zimmerman has described in a four weeks' human embryo two small vesicles near the anterior extremity of the fore-gut, and which he regards as representing Seessel's pocket.

The proximal or buccal extremity of the canalis cranio-pharyngeus does not usually disappear entirely, but persists as the pharyngeal hypophysis (Rachendach-hypophyse). This is a small cylindrical structure, 3 to 5 mm. in length, lying in the mid-line near the junction of the nasal septum with the roof of the pharynx. The histological structure of this body recalls that of the pars anterior of the pituitary.

Remnants of the buccal epithelium are not uncommonly discovered in the neighbourhood of the pituitary gland. Luschka described such areas in association with the infundibulum, and Erdheim stated that some degree of epithelial cell grouping can be detected near the

pituitary in 80 per cent. of adults. He stated that epithelial cells are to be found in two chief positions : an upper group situated on the anterior aspect of the infundibulum near its origin from the brain, and a lower group in the angle between the inferior end of the infundibulum and the anterior lobe. These regions correspond with the site of attachment of the primitive canalis cranio-pharyngeus. Arai and Dandy and Goetsch have described a third epithelial anlage lying beneath the pituitary glands of cats and dogs, occupying a pit in the floor of the sella turcica (the parahypophysis).

Meanwhile, other changes have been taking place in the ectoderm of the stomodæum. A ridge has appeared early in fœtal life which is

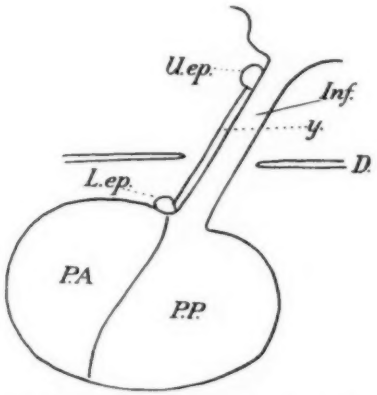

FIG. 1.—Diagram illustrating the two chief sites in which epithelial relics are found : *Inf.*, infundibulum ; *U. ep.*, upper group of epithelial cells ; *L. ep.*, lower group of epithelial cells ; *y.*, single layer of anterior lobe cells running up in front of the infundibulum ; *D.*, dura mater : *P.A.*, pars anterior ; *P.P.*, pars posterior.

known as the tooth band. At ten places along this ridge, separated by regular intervals, invaginations of the epithelium appear. These buds form in the tenth week goblet-shaped bodies connected by a narrow stalk with the surface epithelium ; they are the " enamel organs." Their base then becomes flattened and later concave, so as to form a sort of cap over the primitive dentine organ. Four types of cell structure are now recognizable in the enamel organ :—

(1) The external epithelium which is continuous with the rete Malpighii of the ectoderm. (2) The stellate reticulum which constitutes the pulp of the enamel organ. (3) The stratum intermedium which forms the base of the organ. (4) The internal epithelium which is

really a continuation of the external epithelium, but is restricted to the base of the enamel organ.

As development proceeds, the neck of the enamel organ atrophies and disappears. The external epithelium in all probability constitutes the cellular layer of Nasmyth's membrane. The stellate reticulum consists of large stellate cells with very definite nuclei and branching processes attached to the cell margins. There is some uncertainty as to the function of this reticulum; Tomes, Eve and others regard it as a tissue which has undergone colloid degeneration; Rose on the other hand believes that it supplies nutriment to the growing enamel organ. At a later stage of development the nuclei atrophy. The stratum intermedium is made up of rounded or polygonal cells separated by the outer ameloblastic membrane from the internal epithelium; this layer later disappears. The internal epithelium forms the ameloblasts or adamantoblasts—the enamel-forming cells. In appearance they consist

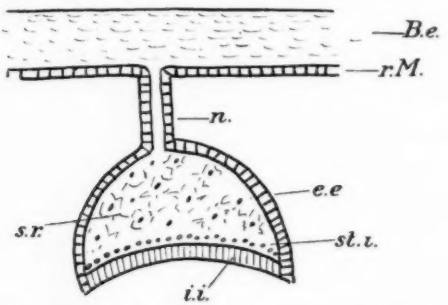

FIG. 2.—Schematic representation of the enamel organ. *B. e.*, buccal epithelium; *r.M.*, rete Malpighii; *n.*, neck of enamel organ; *e.e.*, external epithelium; *s.r.*, stellate reticulum; *st. i.*, stratum intermedium; *i. i.*, internal epithelium (or ameloblast layer).

of a single layer of columnar cells, hexagonal on cross section, with very distinct oval nuclei lying in the distal portion of the cell. Within the nuclei a fine network and a definite nucleolus can be determined by appropriate staining. A system of protoplasmic fibrils may occasionally be detected, running in the long axis of the cells.

The function of the ameloblasts is intimately bound up with the production of enamel, although the exact mechanism by which this is effected still remains in doubt. Three views are predominant as to the exact method of amelogenesis:—

(1) According to J. Jones, Waldeyer, Kölliker and others, the ameloblasts are actually converted into enamel rods. (2) C. Tomes,

Leon Williams, Andrews and Schäfer believe in an actual secretion of of the ameloblasts, which produces enamel. (3) Schwann is of opinion that enamel rods are produced by growth of the ameloblast at the end next to the formed enamel; the new growth in the younger part is calcified as soon as it is formed.

The ameloblasts commence to function in the fourteenth week of fœtal life in the milk incisors; their activity is continued into the first few years of infancy. After the process of enamel calcification is completed, the ameloblasts disappear, although there is some evidence to suggest that they persist in an altered form as part of Nasmyth's membrane.

Personal Cases.

Case 1.

Cystic adamantinoma, largely suprasellar but partly intrasellar, arising from the anterior surface of the infundibulum, in a woman aged 27. *Onset* 10 *years previously with dimness of vision, diplopia and cessation of the menses. Infantile appearance; increasing adiposity and hairlessness for six months. Drowsiness. Enlarged sella with shadows of calcified areas (X-ray). Optic atrophy. Operation: evacuation of the cyst and partial removal of the cyst wall (frontal route). Death with hyperpyrexia and air-hunger twelve hours later.*

Louisa N., aged 27, was admitted to the National Hospital under the care of Dr. Adie. She complained of failing vision, increase in weight and drowsiness. Ten years ago her periods (which had commenced at the age of 12) ceased and did not return. She then had attacks of double vision, "saw two clocks when there was only one," and she noticed that the sight of her right eye was becoming dimmer. The patient thought the vision in the right eye improved for a little, but three months later the left eye began to fail. Since then the vision in both eyes had steadily deteriorated, and at the time of examination very little sight remained in the left eye. One year ago the diplopia ceased. Six months ago the patient noticed that she was gaining considerably in weight. Her hands were becoming fatter, but there was no change in the width of the hand or the length of the fingers. A ring that she was wearing had to be removed by the doctor. Her hair commenced to come out "in handfuls." For six months she had had severe frontal and occipital headache. The pain seemed often to be just behind her eyes, and her eyes felt as if they were being pushed out and her temples as if they were being gripped in a vice. These headaches were felt at all times of the day and night, and were frequently accompanied by vomiting which did not relieve the pain.

She had been very drowsy for the past six months, and her relatives stated that it was almost impossible to wake her in the mornings. She would fall into a deep sleep at any time of the day when she sat down ("she sits down to rest her head and five minutes later she is sound asleep"), and she would frequently

nod over her food. The patient had noticed some impairment of her memory for recent events during the past three months of her illness.

Her previous health had been good and the family history revealed nothing significant.

On examination the patient was an intelligent bright girl. No abnormal drowsiness was observed during the examination. The physique generally was that of a girl aged 17. Weight 131 lb. Height 63 in. There was a moderate increase in the subcutaneous fat, chiefly in the regions of the pelvic and shoulder girdles, and at the nape of the neck. The face had a puffy, doughy appearance, but the features were small and the nose and lips delicate. The complexion was pale, slightly yellowish and translucent, and the skin was smooth, dry, and of normal thickness. The hair of the eyebrows, pubes and axillæ was entirely absent, the hair of the scalp thin, short, and silky. The hands and feet were plump and small, the fingers tapered considerably. The nails were longitudinally furrowed and the lunulæ were absent. The tongue was small.

To test substances smell was unimpaired in both nostrils. With the right eye patient could count fingers at 6 in., and with the left at 24 in. Only a small area of the visual field remained in either eye; this was situated in the upper nasal quadrants and was larger in the right than in the left eye. Both optic discs were pale and the lamina cribrosa was visible. The optic atrophy was more severe in the right eye. The edges of the discs were clear and the retinal vessels were somewhat larger than normal. The pupils were central, circular, and of equal size, both reacted sluggishly to light, directly and consensually, and on accommodation. Because of the visual defect the left eye did not converge fully when the patient attempted to accommodate, The external ocular movements were otherwise full and tests with coloured glasses revealed no diplopia. The other cranial nerves were normal.

The motor and sensory functions were normal. The abdominal reflexes were brisk. Both ankle-jerks were sluggish. The right plantar response was equivocal and differed from the left which was definitely flexor.

The other systems revealed no abnormality. The systolic blood-pressure was 110, the diastolic 45 mm. Hg. The average total daily output of urine was 35 oz.

Lateral stereoscopic X-ray pictures of the skull showed that the pituitary fossa was much enlarged and the posterior clinoid processes almost completely absorbed. Three shadows were visible; one large circular shadow 4 mm. in diameter lying just above and behind the sella, and two smaller shadows lying within it. The fossa at its maximum antero-posterior diameter measured 22 mm. Viewed with the stereoscope the sella seemed shallow and opened up from above by a pushing forwards of the left anterior clinoid process and absorption of both posterior clinoid processes. The floor of the sella was neither deepened nor hollowed out.

The resting blood-sugar was 0·08 per cent., the maximum rise within normal limits (0·17 per cent.), but the descent to normal slow (150 minutes).

While in hospital the patient showed signs of being abnormally drowsy, and on two occasions fell asleep over her food.

Operation: Fourteen days after admission the suprapituitary region was explored by Mr. Sargent (right frontal osteoplastic flap). A cyst was exposed in the suprapituitary region, which flattened the right optic nerve along its outer wall. The capsule was incised and a quantity of yellow, frothy fluid evacuated. A considerable amount of solid tumour substance and part of the capsule was removed by suction.

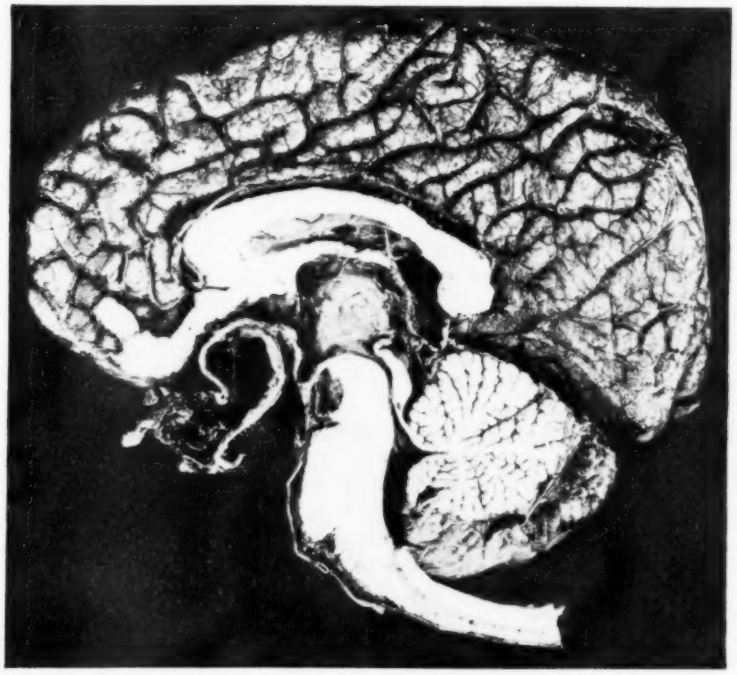

FIG. 3.—Illustration of the right half of the brain in Case 1. The tumour is visible as a large cystic neoplasm pushing upwards the floor of the third ventricle. The more solid portions of the tumour were mainly removed at operation, and lay in the antero-inferior portion of the mass. The pituitary body itself is not visible.

Eight hours after the operation the patient developed air-hunger, the temperature rose to 105·2° F., she became restless and delirious, and twelve hours later she died.

A post-mortem examination was performed fourteen hours after death. A large supra and intra-sellar semicalcareous cystic tumour was found. The brain itself was normal and there was no hydrocephalus. The sella was much enlarged and the posterior clinoid processes absent. A hard calcareous mass which was adherent to the upper and posterior part of the sella was removed

along with the basi-sphenoid. The intraseller part of the tumour with a large part of the pituitary gland had been removed at operation.

The tumour was sausage-shaped and measured 4 cm. in its antero-posterior and 2 cm. in its transverse diameters. It was situated largely above and in front of the optic chiasma, and the splayed-out optic nerves wound on either side of the lower part of the growth. The tumour took origin from the upper and anterior wall of the infundibulum.

Above, the growth was surrounded by a thick capsule which was in part calcified. The rounded upper end of the tumour pressed backwards and upwards on the anterior half of the floor of the third ventricle, invaginating the orifice of the infundibulum into the ventricular cavity. The tumour was adherent to the anterior part of the tuber cinereum and further forward it lay beneath and pushed upwards the gyri recti of the frontal lobes. At no point had the tumour broken through the floor of the third ventricle. The posterior half of the ventricular floor was free and the corpora mamillaria were intact.

Below, the capsule of the tumour was deficient anteriorly, part of it having been removed by the operation, and the growth was adherent to the sella turcica behind where the hard calcareous mass was situated.

The interior of the tumour was largely cystic and filled with yellowish albuminous fluid and blood-clot. The upper part of the tumour was almost entirely cystic, the only solid portions were smooth, calcified areas which appeared as thickenings of the wall of the cyst. The cyst wall of the lower part of the tumour was shaggy and several calcifying villous processes projected into the lumen. This portion of the tumour was more solid.

The pituitary gland itself seemed to have been largely destroyed at the operation.

Histologically the portion of tumour removed at operation was a typical adamantinoma, with considerable hyaline change, calcareous deposition, and actual bone formation (see figs. 5 and 7).

Case 2.

Semicystic adamantinoma, largely suprasellar, arising from the anterior surface of the infundibulum in a boy aged 7. *Infantile, adipose, delicate appearance. Drowsy. Failure of vision for four months. Urticaria three months ago. Squint three weeks ago. Secondary optic atrophy. General symptoms of increased intracranial pressure. X-rays showed enlarged sella, with a suprasellar shadow. Operation in two stages: partial evacuation of the cyst, which contained cholesterin. Collapse and death twelve hours later.*

Eric H., aged 10, was admitted to the National Hospital, under the care of Dr. Gordon Holmes. His mother stated that during the past year he had become considerably stouter. Four months ago he complained of frontal headaches, worse in the evening when he returned from school, sometimes coming on through the night and making him cry out with pain. Three months ago he had an attack of frontal headache and severe vomiting.

which was associated with nettle-rash on the body and limbs, lasting thirty-six hours. During the first part of this attack his eyes were suffused and ran with water. Since then he had complained of "heat waves and flushes of heat." Two months ago he had an attack of headache and vomiting, lasting twelve hours, in which his pupils were dilated and his eyes watered. He was examined by an oculist at this time and his vision was found to be $\frac{6}{6}$ in either eye. Three weeks ago the left eye began to turn in, and he complained of double vision. His hands were always cold and he complained of stiffness at the back of his neck. During the last week he had become increasingly drowsy. There was no frequency of micturition.

On examination the patient was so drowsy that it was almost impossible to rouse him. His weight was 54 lb. and his height 46 in. His general appearance was infantile, and suggested a child of six or seven years. The head was large, antero-posteriorly and laterally, the face small, with fine features and good colouring. The neck was short, the trunk had a rather feminine contour, with moderate subcutaneous padding. The mammæ were rounded, but not remarkable, the suprapubic fat rather increased. The hands and feet were small, the fingers short and tapering. There were no axillary or pubic hairs, the eyebrows and hair over the scalp were soft and silky; on the outer side of the forearms near the elbows were a few longish brown hairs. The genitalia were normal. The voice was hoarse and there was some degree of trismus. Systolic blood pressure was 108 mm. Hg.

There was no anosmia with test substances. Right vision $\frac{6}{36}$, left vision $\frac{6}{60}$. The patient counted fingers at bed-length with the right eye better than with the left. The fields showed to rough tests a bitemporal hemianopsia, more marked in the left eye; there was some contraction of the nasal field in the left eye. The patient was so drowsy that it was impossible to chart the visual fields. The right optic disc was swollen to 3 D, the left optic disc was in a state of consecutive optic atrophy and the vessels were constricted. The pupils were equal and widely dilated, and the light reactions were brisker in the right eye. The corneal reflexes were not elicited. The cranial nerves were otherwise normal. The gait was unsteady and the patient walked on a broad base, lurching from side to side.

The motor and sensory functions were normal. The reflexes were normal, but the knee-jerks and ankle-jerks were sluggish. The plantar responses were flexor.

Lateral stereoscopic pictures of the skull revealed an enlarged pituitary fossa, measuring 17 mm. in its antero-posterior diameter. The anterior clinoid processes were visible, but the posterior clinoid processes had been largely absorbed. Above and behind the widened aperture of the sella there was a roughly circular shadow 12 mm. in diameter. Lying within the sella were two smaller millet-seed shaped opacities. The floor of the sella was not deepened. Viewed stereoscopically the sella appeared shallow and broadened posteriorly where the dorsum sellæ was almost absent. The anterior clinoid processes were rarefied, but their anatomical relations were undisturbed.

The cerebro-spinal fluid was clear, colourless, contained two cells per cubic millimetre, 0·005 per cent. glucose and 0·727 per cent. chlorides. The protein was normal.

Operation was undertaken four days after admission by Mr. Percy Sargent. A right-sided parietal decompression was performed. The dura, which was found to be under moderate tension, was opened. After this operation the papillœdema increased by 1D. in the right eye and 2D. in the left eye, but the visual acuity improved (right and left $\frac{6}{24}$). The patient had attacks of shivering without any rise of temperature.

Fourteen days later the pituitary region was approached by the fronto-orbital route from the left side. The left lateral ventricle was tapped and 14 oz. of clear, cerebro-spinal fluid removed. The tumour was exposed lying chiefly in the suprasellar region, pressing anteriorly and flattening the left optic nerve. The capsule of the tumour was incised and a quantity of dark yellow, blood-tinged fluid withdrawn. The solid contents of the tumour were partly broken up and removed by suction. The fragments showed a few glistening cholesterin crystals. The patient never fully regained consciousness after the operation. He took fluids by mouth with difficulty. Twenty hours after the operation he collapsed and died. The temperature was subnormal during the post-operative period.

Post-mortem.—An autopsy was made six hours after death. The brain itself was normal apart from slight hydrocephalus. The tumour appeared in the mid-line in the infundibular region, and was about the size of a walnut. It was situated above the chiasma, pressing it downwards. The sella was enlarged and opened up from above and the posterior clinoid processes were flattened backwards by the tumour and partly absorbed. The pituitary body was of normal size, separate from the growth and flattened from above downwards.

The tumour was surrounded by a fibrous capsule, except where it was united to the anterior surface of the infundibulum, from the upper part of which it seemed to arise. This capsule had been penetrated anteriorly and below by the surgeon. The mass measured 3 cm. in its sagittal and 2·5 cm. in its coronal diameters. The upper part of the tumour was fairly solid, but below the growth was semicystic, and contained a highly albuminous yellowish serum with numerous cholesterin crystals and some calcareous matter. The tumour bulged up the whole of the floor of the third ventricle from the lamina terminalis to the corpora mamillaria, but the floor was nowhere invaded.

Histologically the more solid portions of the tumour were composed of typical adamantinomatous tissue lying in an abundant glial stroma (see fig. 8).

Case 3.

Partly cystic, partly solid suprasellar adamantinoma, arising from beneath the capsule of the anterior lobe in a woman aged 35.

Amenorrhœa, great adiposity and falling hair for the past eighteen months. Diplopia and failing vision. Paracentral scotomata, the larger in the right eye.

Slight swelling of the right optic disc. Sella enlarged laterally. Operation: Right subtemporal decompression. Hyperpyrexia, urticaria and death.

Florence S., aged 35, was admitted to the National Hospital under the care of Dr. Holmes. She complained of great failure of vision, increasing stoutness and headache.

Three years ago the patient noticed some blurring of her eyesight when she read and her eyes quickly tired over the print. Eighteen months ago her periods, previously regular, ceased and she began to gain in weight. At that time she weighed 154 lb.; on admission she weighed 226 lb. Eight months ago she began to suffer from severe headache behind her eyes and in the occipital region, always more severe when she awoke in the morning. Her vision was becoming much worse, she had double vision from time to time and occasionally she vomited when the headache was severe. She noticed that the hair of her scalp was becoming thinner. Two weeks ago she found she was unable to read printed matter or to sew. She complained that the light hurt her eyes, her headaches were greater in frequency and intensity and she had now become enormously stout. She thought that she was passing more urine than formerly.

On examination the patient was extremely adipose; the fat was generally distributed over the limbs, trunk, pelvic girdles and face and neck. The skin generally was fine, dry and soft, the palms rather horny, the nails dry and brittle and longitudinally furrowed. Over the scalp, axillæ and pubis the hair was sparse. Patient was of medium stature, the hands and jawbones small. The face was round and fat, the complexion slightly cyanosed with dilated venules on the cheeks. The mouth was small, the tongue was flabby and decidedly large.

No loss of smell to test substances. Visual acuity: right eye, could not read $\frac{6}{60}$, left eye $\frac{6}{60}$. The fields of vision showed a bilateral scotoma for white, larger in the right eye. In the left eye the scotoma was paracentral, in the right eye (with Bjerrum's screen 10 mm. at 100 cm.) the scotoma was found to overlap the fixation point as far as 4-5° to the nasal side. She was unable to recognize red or green in the region of the fixation point in either eye.

The right optic disc was swollen at its upper margin and the veins were slightly full. The left optic disc was normal. The right pupil was larger than the left. The left reacted directly to light less briskly than the right; both reacted consensually. Slight convergent strabismus and a complete right sixth nerve palsy were present. The right palpebral fissure was wider than the left and the right eye slightly more prominent. A few nystagmoid jerks were seen in the left eye when the patient looked to the extreme right. The sensory, motor and reflex functions were normal. There was no abnormal drowsiness. The systolic blood-pressure was 121 mm. Hg and the diastolic 82 mm. Hg. The average daily amount of urine was 80 oz.

A stereoscopic X-ray picture showed that the sella was broader than normal, but not enlarged in the antero-posterior plane. 100 grm. of glucose given by mouth gave rise to no glycosuria.

Operation (Mr. Sargent) two months after admission. Preliminary right tempero-parietal decompression. There was evidence of great increase of intracranial pressure. No attempt was made to explore the pituitary region. Five days later the patient's temperature rose to 104° F., the body surface became covered with a profuse eruption of giant urticaria and she died.

A post-mortem examination was made eighteen hours after death. A semi-cystic tumour was found in and above the sella turcica, slightly to the left of the mid-line and behind the chiasma which it had pushed forwards. The tumour measured 3 cm. in its coronal and sagittal diameters. Considerable hydrocephalus was present and the cerebral convolutions were flattened and widened. A pressure cone was present. There was very great enlargement of the pituitary fossa, chiefly at the expense of its anterior margins. The sella was broader and deeper than normal and the posterior clinoid processes were pushed backwards.

The tumour appeared to have grown largely from beneath the anterior lobe of the pituitary gland, and it had spread upwards obliterating the infundibulum. Considerable portions of the tumour were solid but the upper part was composed of four large cystic cavities with shaggy walls, containing yellow fluid. The growth involved the whole of the posterior part of the floor of the third ventricle and the corpora mamillaria. The cavity of the third ventricle was largely obliterated behind by the invagination of the tumour which pressed upwards and backwards between the optic thalami; but anteriorly the optic recess of the third ventricle was prominent. The cerebral peduncles were not pressed upon by the growth.

The thyroid was normal, the thymus (mostly fatty tissue) reached halfway down the pericardium. Both suprarenals were healthy. The right ovary was very small and atrophic, and the uterus was smaller than normal though not so small as in the involution of age. Histologically the tumour was a primitive type of adamantinoma, with no calcareous depositions (see fig. 10).

Case 4.

A cystic suprasellar adamantinoma in a child aged 11. *Three years' history of headache, vomiting, and blurred vision. Physically undersized. Bilateral papillœdema. X-ray shows normal sella. Simple decompression operation only. Death three weeks later with hyperpyrexia.*

Douglas, F., aged 11, was admitted to the National Hospital under the care of the late Dr. F. E. Batten.

Two years ago he had an attack of severe frontal headache and vomiting, and was said at this time to have papillœdema. At intervals after this he complained of blurring or mistiness of vision and he was liable to intermittent headache, worse in the morning just after rising. Fifteen months ago the headache became more frequent and severe, and he complained of numbness and tingling in both legs. His vision began to fail. Two weeks ago the patient complained of double vision and had attacks of momentary giddiness during which he would have to hold on to objects of furniture for support.

The patient's previous health had been good. Investigation of the family history revealed that his father died of tuberculosis.

On examination the patient was a small, bright, intelligent child, poorly nourished and looking younger than his age. His weight was 49·5 lb. There was no anosmia with test substances. The visual acuity in the right eye was $\frac{6}{9}$, in the left $\frac{6}{12}$. The fields showed no abnormality to rough testing. The right optic disc presented considerable rather abrupt swelling of the champagne-cork type, measuring 4 D. The veins were tortuous and dilated. The appearances in the left optic disc were similar to those in the right, but the swelling was greater and measured 5 D. The cranial nerves were otherwise normal, except that the tongue when protruded deviated slightly to the left. There was slight difficulty in performing rapid and fine movements with the left upper limb, otherwise the motor, sensory, and reflex functions were normal. An X-ray of the skull revealed no abnormality of the pituitary fossa. The cerebro-spinal fluid contained 0·02 per cent. albumin and five cells (mononuclear) per cubic millimetre.

Fourteen days after admission a decompression operation was performed by Mr. Sargent. The dura was extremely tense and the intracanial pressure very high. After the operation the patient developed increasing flaccid weakness of the left arm and leg, he became very drowsy and complained of photophobia. Three weeks later, after several generalized epileptiform convulsions, the patient's temperature rose to 104° F., and he died.

At autopsy, a large nodular, semicystic tumour was found in the interpeduncular space, pressing on the optic chiasma from above. The pituitary and pituitary fossa were normal and intact. There was considerable hydrocephalus affecting all the ventricles and a pressure cone was present. The tumour appeared to take origin from the upper part of the infundibulum, which it entirely replaced. The surface of the tumour was smooth, and its diameters measured as follows: coronal 2·5 cm., vertical 3 cm., antero-posterior 4 cm. On section it was irregularly cystic in its upper and anterior portions, but the larger part of the tumour was more solid and vascular. The growth extended along the whole length of the floor of the third ventricle, which it pushed upwards. All the tuber cinereum and both corpora mamillaria were involved by the growth, but at no place had the tumour broken through the ventricular floor. Anteriorly the growth extended above the optic chiasma and pressed upwards the gyri recti of the frontal lobe.

The histological appearances were those of a typical adamantinoma (see fig. 6).

Case 5.

Partly cystic, partly solid suprasellar adamantinoma, containing calcium and cholesterin in a boy aged 16. *Mistiness of vision for six months. Infantile appearance. Optic atrophy. Slight weakness of left face and arm. Left lower abdominal reflex absent. Left plantar reflex extensor. X-ray showed suprasellar shadow. First operation, evacuation of cholesterin-containing cyst. Second operation (two months later), removal of contents of cyst, including opaque mass*

shown on the skiagram. Death two and a half months later in coma. No autopsy.

Alfred M., aged 16, was admitted to St. Thomas's Hospital under the care of Mr. Sargent.

Four years ago he began to suffer from occipital and cervical pains. Six months ago these pains became much more severe and were accompanied by frontal headache and giddiness. He noticed at this time that his eyes were misty, and for the past four months his vision had noticeably deteriorated.

On examination the boy was markedly infantile in appearance, the bodily configuration suggesting that of a child of ten years. Height 55 in. Weight 56·5 lb. The hair of the head was normal in quantity and texture, and the eyebrows were normal, but hair was entirely absent over the pubis and in the axillæ. The secondary sexual characteristics were absent. No adiposity. Mentally the boy was bright and intelligent, but somewhat childish.

There was no anosmia with test substances. Both optic discs showed early optic atrophy. A left homonymous hemianopsia was present with some contraction of the nasal field in the left eye. The left pupil was larger than the right, and the right pupil reacted sluggishly to light. The motor, sensory and reflex functions were normal.

An X-ray of the sella showed enlargement of the upper aperture at the expense of the anterior clinoid process, with an irregularly outlined opaque mass above and to the left of the fossa.

The resting sugar was low (0·083 per cent.). The sugar curve showed no hyperglycæmia (0·163), but the fall was delayed (160 minutes).

Progress notes.—Two months later patient had developed signs of slight left-sided weakness. There was left-sided facial asymmetry, the abdominal reflexes tired easily on the left side, and the left plantar response was extensor.

Operation (Mr. Sargent).—Right-sided osteo-plastic flap. A large supra-pituitary cholesterin-containing cyst was found in the suprasellar region. This was emptied by suction, and the opening in the cyst wall closed by a muscle graft. The fluid taken from the tumour was yellowish and contained blood, 2 per cent. albumin, and a large amount of cholesterin in crystalline form (Dr. O. V. de Wesselow).

After the operation the patient improved very considerably for two months; the visual fields showed almost no abnormality, but the patient still suffered from occasional headaches and watering of the eyes. These headaches became more severe and the vision again began to deteriorate. The slight left-sided weakness became more marked, and examination of the visual fields showed a left homonymous hemianopsia with involvement of central vision in the left eye.

Operation (Mr. Sargent).—The cyst was again exposed by opening up the previous incision. Ventricular puncture was performed and 4 oz. of fluid removed. The capsule was found to be tense, and it was opened freely and the contents removed by suction. A small calcified grape-like portion of tumour was removed together with part of the cyst wall.

The patient improved for fourteen days after this operation, then he became very drowsy and slept all day and night. The optic atrophy increased. The bone flap began to bulge and the patient commenced to vomit. Both plantar responses had now become extensor.

Two and a half months later the case terminated fatally. No post-mortem examination was permitted.

The material obtained at operation on this patient showed histologically all the characteristics of a typical adamantinoma with hyaline and calcareous deposits (see figs. 4, 11 and 12).

Case 6.

Semicystic, calcareous, suprasellar adamantinoma in a woman aged 24. *Ten months' history of headache and vomiting. Consecutive optic atrophy. Slow development of bilateral hemiplegia and decerebrate rigidity after a right-sided decompression.*

Florence D., aged 24, was admitted to University College under the care of Dr. Walshe.

Ten months ago she began to suffer from periodic attacks of slight headache and vomiting which, during the past week, had become severe.

The patient was completely blind from consecutive optic atrophy, but she was mentally alert and intelligent and her speech and articulation were normal. The motor and sensory systems presented no abnormality and the tendon reflexes were brisk and equal. The abdominal reflexes were elicited feebly and both plantar responses were extensor. The bodily conformation presented no abnormality.

A right-sided decompression was performed and after this the patient became semi-comatose, and during the two weeks which followed developed a left hemiplegia. Four weeks after the operation, the patient became completely comatose and a condition of double hemiplegia supervened. At this stage, the patient presented all the characteristics of the state of decerebrate rigidity. The last six days of life were marked by a progressive loss of reflex activity and increasing coma. The tendon reflexes disappeared. At intervals the patient had attacks, lasting from fifteen to twenty seconds, in which the head suddenly became retracted, the limbs extended and rigid, the face flushed and the respiratory muscles immobile.

At autopsy a loculated semicystic calcareous tumour was found in the interpeduncular space separating the optic tracts. The pituitary gland itself lay below and behind the tumour and was separate from it. There was considerable hydrocephalus affecting all the ventricles. The growth extended along the whole length of the floor of the third ventricle which it invaginated. At no place had the tumour broken through the ventricular floor. Histologically the growth presented the typical picture of an adamantinoma.

Case 7.

Semicystic suprasellar adamantinoma in a man aged 60. Ten months' history of failing vision. Primary optic atrophy. Bitemporal hemianopsia. Adipose feminine habitus with horizontal distribution of pubic hair and loss of sexual power. Operation (Mr. Sargent): Evacuation of cholesterin-containing cyst. Improvement and collapse three months later. Operation (Mr. Sargent): Partial removal of tumour. Improvement again but relapse and death some months later.

Edward G., aged 60. Seven months previously noted failure of vision in the left eye. Perimetric observations at this time revealed the presence of a bitemporal hemianopsia. The patient had noticed that his weight was increasing and that he had lost sexual power. He was definitely of the female build with horizontal distribution of the pubic hair. There was considerable increase of mammary, gluteal and pubic fatty tissue. The right fundus was normal, the left disc showed primary optic atrophy. R.V. $\frac{6}{6}$, L.V. $\frac{6}{60}$ There was bitemporal hemianopsia involving central vision in the left eye. An X-ray picture of the sella turcica showed deformity of the anterior clinoid processes and slight enlargement of the sella.

Four months later, an operation was performed by Mr. Sargent: Left-sided osteoplastic flap. The frontal lobe was elevated and a very large quantity of cerebro-spinal fluid escaped from around the chiasma. There were certain thickenings and adhesions of the arachnoid round the tumour which evidently caused considerable loculation of fluid in this region. The optic nerve was pale and was running vertically upwards, being pushed forwards and somewhat flattened by the tumour which could be seen on either side of it.

The tumour capsule was incised and a large amount of yellow fluid containing cholesterin crystals escaped and was removed with a sucker. There appeared to be no solid tumour. The chiasma did not come into view. When the cyst had been emptied the optic nerve was seen to have been entirely freed from pressure. A muscle graft was used to close the opening in the cyst. There was no hæmorrhage at all, the operative field never at any time being obscured by blood. The operation was well borne and the patient returned to bed in excellent condition.

Uneventful recovery ensued, with some subjective improvement of vision and relief from headache. Three months later, the vision again began to deteriorate and headaches recurred.

A second operation was undertaken by Mr. Sargent. The flap of the previous operation was turned down and the cyst emptied. A small window was cut out of the tumour wall anteriorly to prevent re-accumulation. Recovery again took place and the patient returned home. It was learned some months later that his symptoms had returned; this relapse was fatal. There was no autopsy.

Sections of tissue removed from the growth at operation showed the structure of a typical adamantinoma.

Pathological Considerations.

The epithelial tumours of the supra-pituitary regions originate in relics of the embryonic canalis cranio-pharyngeus, and they present an extraordinary diversity of consistency, structure and appearance. They display a great variability in rate of growth and in degree of malignancy. In a proportion—possibly in the majority of these growths—areas are demonstrable in which the epithelium has assumed the characteristics of the embryonic enamel organ, and in such areas there is a striking resemblance to the soft variety of epithelial odontomes of the jaws.

The main histological structure of these neoplasms is of a solid epithelial tree with branching and anastomosing off-shoots, lying in a glial or fibrous tissue stroma. Hydropic degeneration leading to cyst formation, and areas of keratinization, calcification, and colloid deposition are commonly present. There is usually a glial tissue reaction around the neoplasm.

The adamantinomata are fairly constant in size, position and macroscopic appearance. They may attain the size of an orange, but they are usually no larger than a walnut. The shape is, as a rule, regularly spherical or ovoid.

The anatomical relationship varies with the exact site of origin; adamantinomata arising from the upper cluster of epithelial cell rests lie above the diaphragma sellæ; the pituitary gland appears to lie quite separate from the tumour, in an antero-inferior direction. With increasing growth the tumour extends more and more upwards, pushing before it the floor of the third ventricle. In some instances the tumour actually fills the whole cavity of the ventricle and insinuates itself between the optic thalami and the caudate nuclei of the two hemispheres, pushing them laterally, and encroaching upon the under aspect of the corpus callosum. The upgrowth of the tumour usually carries with it on its upper surface an attenuated and distorted anterior communicating artery. The optic chiasma lies anteriorly to the tumour and below it, and pressure is therefore exerted upon it in a downward and forward direction. The posterior clinoid processes become absorbed and the sella turcica is converted into a shallow open bowl. Posteriorly, the growth covers the posterior perforated spot and the corpora mamillaria. Adamantinomata, which arise from the lower set of epithelial cells, grow primarily within the sella, deepening it in all directions. The postero-superior wall of the sphenoidal sinus becomes convex owing to the invagination of the anterior wall of the

sella turcica and the pituitary gland is flattened into a disc-shaped cap, which lies behind and below the main tumour mass. Upward extension of the tumour tends to evert the anterior and posterior processes and to push up the dura of the diaphragma sellæ. Pressure is therefore exerted upon the inferior and posterior aspects of the optic chiasma. In the more malign types of adamantinoma, the erosion of the basisphenoid is much greater, and infiltration of the dura and the base of the brain by the growth is a conspicuous feature.

The main points in the anatomy of the adamantinomata of both sources may be crystallized by stating that the mass lies below the brain, above the pituitary, behind the chiasma, and within the circle of Willis.

Transection of the tumour usually reveals that it is made up of numerous cysts of various sizes, which lie within a stroma of variable nature; the appearance on section resembles a piece of conglomerite. Occasionally the growth is a unilocular cyst; at other times no cysts are visible to the naked eye. The contents of the cyst are variable; here and there are areas of viscid colloid material of a brown or green colour, whilst other cysts contain an oily, golden-yellow fluid in which numerous glistening cholesterin crystals appear. The cyst walls are relatively thick and are made up of a tough fibrous or fibro-chitinous substance. The inner aspect of the cyst wall may be smooth and vitreous, but more commonly it is roughened by the outgrowth of numerous papilliform excrescences. Sometimes extravasations of blood stain the cyst walls, which vary in appearance from smooth red plaques in the recent cases to the older granular brown patches.

The solid portions of the tumour are of mixed consistency, varying not only in different specimens, but also in different portions of the same specimen. The main portions are soft, spongy and vascular, and of a deep red colour. The occurrence within the softer connective tissue of areas of hard consistency, formed of calcification or even of bone, is very characteristic. These areas cause a characteristic gritty sensation when they are cut across, and in the more solid varieties transection may be a matter of great difficulty.

Parallel with the varying macroscopic appearance presented by these tumours, there is a similar diversity of histological structure. The neoplasms as a whole consist of an epithelial growth which is very prone to cyst formation, lying in a stroma which undergoes all manner of abnormal cell growth and decay. The presence of a single row of columnar cells, corresponding in structure to the embryonic

ameloblasts, and arranged in a palisade formation at the periphery of the epithelial masses, is the criterion for diagnosing the tumour as an adamantinoma. Ameloblasts may not be a conspicuous feature in a given section, though usually the main epithelial arrangement of the tumour is identical with that in the softer variety of epithelial odontomes. A great variability in the proportion between connective and epithelial tissue is found in different specimens; in some the amount of stroma may be negligible.

A closer histological study of these tumours may conveniently be pursued by examining them under three separate heads; the epithelial elements, the connective tissue stroma, and the glial tissue reaction in the surrounding structures will be studied individually.

The epithelial masses are made up of branching and interlacing columns or trabeculæ, which are in the main, solid structures. As viewed on cross-section they are circular, ovoid, lobed, or crenated areas, composed of a distinctive cell arrangement and appearance. The basal or peripheral cells are long, slender columnar cells, arranged with their long axes in parallel series, each cell being in close contact with its neighbour. Such an arrangement is aptly spoken of as a "palisade formation." Each cell is approximately three to four times as long as it is broad, and on transverse section it is square or pentagonal. There is but a single row of these cells, and they are set in a direction diametric with each epithelial mass. The nuclei are oval and darkly staining, situated in the centre of the protoplasm, the greatest diameter lying in the long axis of the cell. In some cases it is possible to discern intranuclear fibrils, and there is a well-defined nucleolus. The cells correspond in structure and arrangement with the ameloblast cells, which constitute the internal epithelium of the primitive enamel organ, and which form the peripheral cell elements of epithelial odontomes. The finding of these adamantoblast cells is a *sine quâ non* in the diagnosis of pituitary adamantinomata.

Immediately beneath the ameloblastic layer is an intermediate zone, comprising two or three rows of cells. These are rounded or polygonal in shape, containing a centrally placed, well defined nucleus, which stains less darkly, however, than the ameoblasts. The protoplasm stains a faint yellow with van Gieson's stain. In some specimens this cell layer is not easily defined from the main epithelial mass, though usually it is present to some degree. This zone corresponds to the stratum intermedium of the enamel organ.

Innermost of all lies the main cell system of the epithelial masses.

The individual cells are larger; in shape they may be rounded, but more usually the outlines are angled off so as to form triangular or prismatic-shaped structures ("Stachelzellen"; "Riffzellen"). The nuclei may be circular, but are usually reniform, and are centrally placed. They are somewhat small in relation to the amount of protoplasm. They do not stain as well as the others, though the protoplasm takes on a deeper tint than in either the peripheral layer, or in the intermediate zone, with appropriate technique it is possible to distinguish slender protoplasmic bridges connecting the periphery of adjacent cells. The general appearance of these cells recalls the prickle cells of the rete Malpighii of the skin, but the former differ in their smaller size and in the presence of broader intercellular channels. There is a much closer analogy between these cells and those of the stellate reticulum of the enamel organ ("Gallertgewebe") and they may well be referred to as the "stellate cells."

Although the typical conformation of this inner cell mass is that of a collection of loosely packed cells in the smaller epithelial systems, the cells tend to display a slightly different arrangement. They may appear a little larger and more slender, and tend to be arranged in groups, each individual cell member of which is placed in the same direction; thus, in one area the cells may run almost horizontally to the epithelial mass, and next to it may be an area in which the cells are at right angles; in other places there is even a tendency towards a whorled arrangement. A well-marked example of such cell clustering is faintly reminiscent of the arrangement of the short hairs at the back of the neck. Similar clustering may be seen in the cells of meningeal endotheliomata (see fig. 4).

This resemblance is still further enhanced by the formation of cell nests or *globes épidermiques* within the inner cell mass. These bodies are made up of a small whorled system of peripherally flattened cells, which are arranged in a spiral form as in a catherine-wheel. The innermost cells tend to preserve their rounded outline. In some instances these whorled systems become a little flattened so as to appear as pagoda-like structures ("Chinesischen Tempelturm"). Keratinization may set in at a later stage within these globes, so that the cell becomes still more flattened, until finally the nuclei and cell outlines disappear. These horny globes probably correspond with the cell nests, or cancroid pearls characteristic of epitheliomata (see fig. 5). Keratinization is not a common feature of these tumours, and the globes usually remain cellular; nor is it usual to encounter

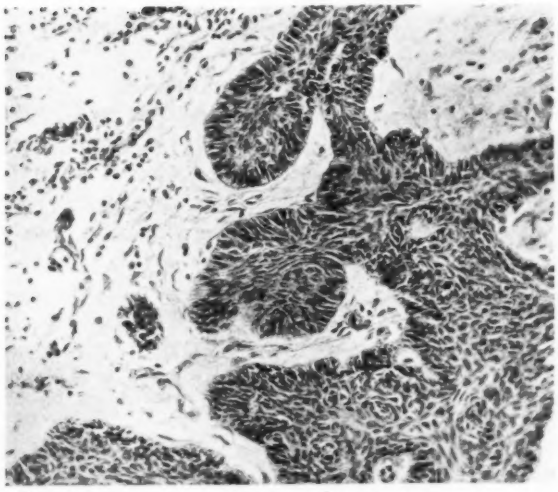

FIG. 4.—High-power view of tumour from Case 5. The tendency to a "whorled" arrangement of the stellate cells is well marked.

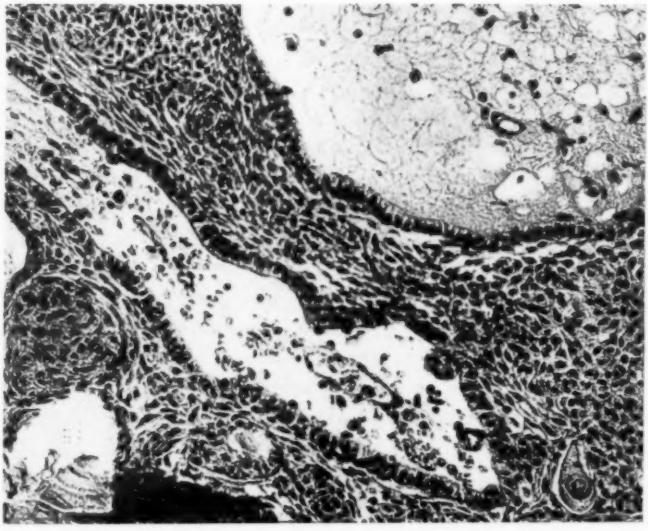

FIG. 5.—High-power view of tumour from Case 1. A cell nest is present, lying adjacent to a cystic cavity. × 230.

eloidin granules within the cells of the nests, or of the neighbouring epithelium. Erdheim, and later Jackson, have both been emphatic that kerato-hyalin granules are not demonstrable in the adamantinomatous type of hypophyseal duct tumours; in the cases reported by Strada and Duffy, however, these granules were present in large numbers.

Duffy speaks of an external limiting membrane lying peripheral to the ameloblastic layer. He calls this the membrana propria, and he states that it is possible to discern vestiges of a greatly flattened cell nucleus in this membrane. We have been unable to satisfy ourselves as to the presence of any such membrane in the majority of our specimens.

In addition to the cell nests other structures are found within the epithelium. Of these the most important are cysts; these are usually very numerous, are of all sizes and are of varying sources of origin. The cell contents too are variable. Three main types of cyst formation can be distinguished within the epithelial mass:—

(1) Small irregular-shaped lacunæ lying between the individual cells of the inner mass. They are an exaggeration of the potential intercellular clefts, and are the result of hydropic distension of the stellate cells with subsequent rupture. In this way there is formed a cavity lined by an irregular jagged margin of distended stellate cells, and containing a clear, colourless muco-albuminous fluid (fig. 6). This type may be referred to as the hydropic cyst and corresponds to the *cavité de désintégration centrale* of the French.

(2) Colloid cysts, which have their origin from droplets deposited or secreted between the cells of the inner mass. With increase in the amount of colloid collection, the cells are further separated until there is formed an ovoid or circular cavity. The walls are composed of a single layer of flattened cells, which in the smaller cysts lie end to end around the cavity. In the larger cysts, however, the living cells tend to be square or columnar in shape, and to be arranged side by side. In most instances the walls are irregularly crenated, and papilliform projections intrude into the centre of the cysts. Regularly circular cysts are as a rule uncommon, though in Case 3 they constitute the majority. The frequency with which colloid cysts are encountered varies widely with different specimens. In some, as in Case 3, almost all of the cysts contained colloid, and the main bulk of the neoplasm is made up of these spaces. In other specimens (e.g., Case 5) the colloid containing spaces are relatively infrequent.

(3) Clear circular empty spaces which constitute the majority of the

cavities in certain specimens (e.g., Cases 1 and 5). These are contained within the centre of the epithelial masses and each mass contains several such cysts. The lining membrane is composed of a single layer of square columnar epithelium accurately arranged around the cavity. The outlines are regular and usually circular. The origin of these spaces is not clear; the lining epithelium resembles a layer of flattened ameloblastic cells rather than stellate cells of the inner masses. It is unlikely that these cysts represent a dilatation of any central cavity in the epithelial masses because it is the rule to meet with three or four

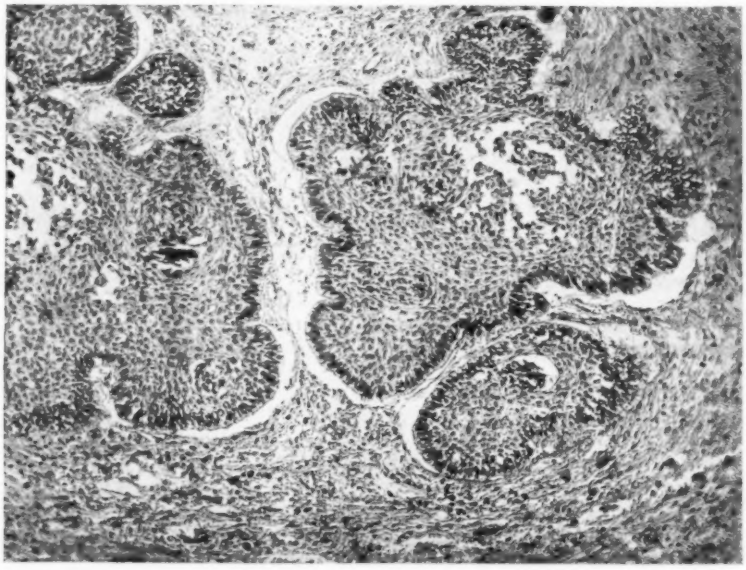

FIG. 6.—Section of tumour from Case 4. In the centre of the two largest epithelia masses commencing liquefaction cysts are plainly visible. × 100.

or even more such cysts within each epithelial mass. One noticeable feature which may be of importance is the fact that the larger masses alone contain the cysts. It is possible, therefore, that these cavities arise from inclusions of ameloblastic cells within the main trunk of the epithelial tree; degeneration cysts are formed which in turn give origin to daughter cysts; the resulting arrangement, therefore, conforms to that encountered in papillary cyst-adenomata of other regions. The lining cell layer probably corresponds to the external epithelium of the enamel organ.

The viability of the epithelial elements in the adamantinomata is very limited, and all stages of dying and dead epithelial cells are encountered. The cell nests probably represent the early stages of a degeneration process.

Various types of morbid change arise—hydropic and calcareous. Around the areas of necrosis multinucleated phagocytes or foreign body giant cells are seen, with their surfaces towards the dead tissue hollowed out; effete particles and calcareous granules may be visible within the substance of these giant cells. Calcified areas are extremely common in these tumours; they arise by a deposit of irregularly shaped lime granules in the periphery of the necrotic areas; later

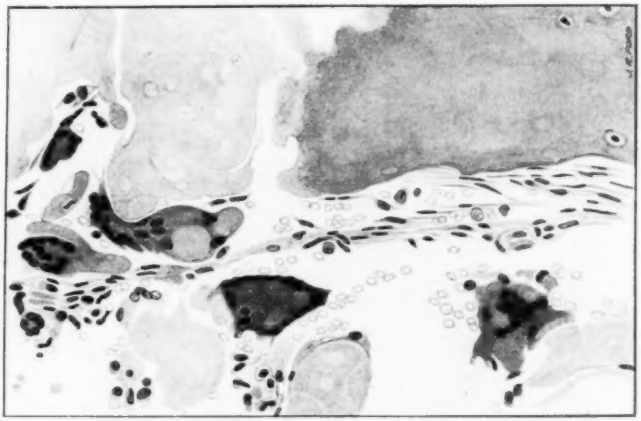

FIG. 7.—High-power drawing of portions of tumour from Case 1. Large areas of bone are visible in the upper half of the illustration, bounded by a layer of fibroblasts and osteoblasts. Five or six multinucleated giant cells are also present.

these granules coalesce and gradually fill up the area from without inwards. Tissue reaction around these masses produces fibroblasts, which, under the influence of the dissolved-out calcium of the epithelium, become osteoblastic. In this way irregular areas of actual bone are formed, commencing in the periphery of the necrotic areas. This phenomenon is analogous to the bone replacement occasionally encountered in calcified epitheliomata of the skin, a process which has been thoroughly studied by Nicholson [9]. Bone replacement is not a common feature of adamantinomata; Erdheim noted it in one only of his cases, and Duffy in one also; it was present in abundance in Case 1 of our series (fig. 7).

The bone appears as lobed or crenated masses lying independent of the epithelial structures, surrounded on all sides by the connective stroma. In the immediate periphery numerous giant cells are seen; some of them are uninuclear, but the majority are multinucleated. Some of these cells are healthy and in full function, being seen to contain particles of foreign matter; others, however, are in all stages of cytolysis, the protoplasm being swollen and cloudy and the nuclei faint and eccentric.

Here and there in some of the spaces areas are found which, though obviously made up of epithelial elements, fail to present the regular arrangement characteristic of the adamantinomatous masses. Such areas are formed of aggregations of columnar cells which still show some faint resemblance to the mature ameloblasts. There is a recognizable attempt at a palisade arrangement, which, however, is irregular, and instead of the typical single layer of such cells there are three, four, or even more rows. These distorted epithelial cells are particularly common in close proximity to the larger areas of myxomatous or calcareous degeneration. It is possible that these areas really represent the cortex of an epithelial mass sectioned obliquely and then viewed from above. In this way the ameloblasts would appear distorted and arranged in several rows.

The stroma of these tumours is comprised in characteristic instances of collections of young fibrous tissue surrounding the epithelial masses, and containing traces of various types of degenerative and regenerative débris. The nature of the connective tissue varies, however, within wide limits in different specimens, and also in different parts of the same specimen. There is a diversity also in the proportion of epithelial to connective tissue element, which again varies not only in different specimens but in different portions of a single tumour.

Ordinarily the stroma is made up of strands of fibroblasts which run in a direction tangential to the epithelial masses; cells in varying degrees of maturity are present, ranging from short spindle-shaped bodies with distinct nuclei to elongated slender fibrils with flattened, indefinite nuclei. These fibrils may assume a regularly parallel alignment at right angles to the epithelial masses, but more commonly they are arranged in no definite order and appear as a loosely-packed interlacing network. There is a great tendency for the cohesion between individual fibrils to be loosened, so that separation is very common and gaps and cavities appear throughout the connective tissue.

In some specimens, as for example our second case, the supporting tissues are almost entirely made up of neuroglia. Fibrous tissue elements are in such instances conspicuously absent. Figure 8 illustrates the nature of the stroma in this case, and in such instances the glial matrix is often far more abundant than the epithelial elements.

Small round cell infiltration of the stroma—patchy in distribution—is a not uncommon finding, and appears to bear no constant relationship either to blood-vessels or to proximity of necrotic areas. Red blood-corpuscles are not uncommonly encountered in the stroma.

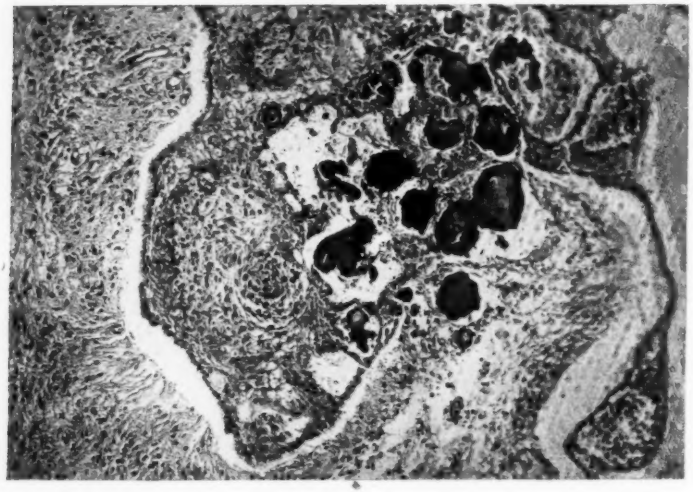

FIG. 8.—Section of tumour from Case 2. There are several circular calcareous areas lying at the periphery of the cell masses. The innermost cells display a variety of regressive changes, and here and there cell nests are visible. The matrix is glial in character. × 100.

Frequently the necrotic epithelial elements of the tumour wander out from the interior of the cell masses, and appear as isolated fragments within the stroma. Such bodies display every variety of morbid change. Thus, one encounters isolated horny cell nests lying like islands in a sea of connective tissue. Such cell nests are invariably keratinized, and are frequently calcareous in part. Large areas of myxomatous matter are formed by the coalescence of smaller clumps of necrotic epithelial cells. Many of the cells exhibit intraprotoplasmic lipoid changes, leading to the liberation of highly refractile yellowish crystals of cholesterin.

In the vicinity of these wandering necrotic elements, giant cells are always present in greater or less degree, some containing a single nucleus, but most of them containing many. The multinucleated giant cell nuclei are deeply-staining oval bodies which are found more towards the cell periphery. Such cells are obviously phagocytic in function (fig. 7).

Cyst formation occurs on a lesser scale within the stroma; the contents are muco-albuminous or colloid. In the smaller cysts the walls are irregular, being formed of connective tissue cells themselves, the cysts being in fact little more than exaggerated intercellular gaps. The walls of the larger spaces are regular and smooth, and are made up of flattened stroma cells.

In some of the more malignant adamantinomata originating from the lower group of epithelial relics, the tumour may contain elements from the anterior lobe of the hypophysis. Thus, in Duffy's second case, chromophobe and chromophil (both eosinophil and basophil) cells were present. No such hypophyseal invasion was found in our series. The stroma carries an abundance of large thin-walled blood-vessels; no nerve elements could be detected in any of our specimens.

In contradistinction to the actively growing epithelial portions of the tumour, there is a distinct reactionary glial proliferation, which requires consideration. This neuroglial overgrowth is met with in the central portions of the more solid varieties of adamantinomata, and augments the fibrous connective tissue. In a few cases, as in Case 2 of our series, the bulk of the tumour is made up of glial tissue, the epithelium appearing at infrequent intervals as solitary islets. Cystic spaces are sometimes seen as irregular cavities filled with yellow fluid; such cysts are due to liquefaction of the neuroglia.

Glial proliferation is also seen around the tumour, forming a sort of capsule. Teutschlaender considers that the tissue reaction of the surrounding structures is a response to an actual chemical irritant set up by the retrograde products in the tumour. Transection through the capsule reveals a definitely laminated system of connective tissue elements, composed externally of neuroglia and internally of fibrous tissue. Within these coverings there is usually a fine epithelial stratum made up of two or more layers of columnar epithelium, the nuclei of which are pale and oval, and lie within a yellowish cytoplasm. Extravasations of red blood-cells are frequently visible between the epithelial and fibrous layers, and in this same situation calcareous or hyaline plaques are common.

It is obvious, therefore, from the histological picture of these tumours that the adamantinomata belong to the group of hypophyseal duct tumours of epithelial origin (Hypophysenganggeschwülste of Erdheim). The general conformation belongs to the papillary cystic neoplasm, the main diagnostic criteria being the single-layered columnar ameloblasts arranged in palisades, surrounding the area of stellate epithelial cells. Cyst formation, the presence of epithelial cell nests and calcification are unessential though very common features.

FIG. 9.—Section of a case of epithelial suprapituitary tumour not adamantinomatous in nature. The cells show an obvious difference in character and arrangement, being circular and loosely packed. The basal ameloblast layer is absent, being represented by two or more rows of cubical cells. × 100.

Various types of grouping have been attempted in these epithelial duct tumours. Erdheim classified them as malignant or benign, but such a division is artificial. More scientific is the grouping suggested by Duffy. He isolates the cysts arising from the walls of the primitive cavity of Rathke's pouch, which is represented in the mature pituitary by the cleft between the anterior and intermediate parts. The remaining varieties he treats in three categories: (1) The benign squamous epithelial papillary cyst, or intracystic papilloma of the

hypophysis or infundibulum; (2) malignant spindle-celled solid tumours; (3) adamantinomatous, cystic, or solid tumours. Of the above groups, No. 2 is excessively rare, comprising—according to Duffy—five recorded cases only. Group 3 is probably the commonest of all the types.

Duffy did not emphasize the fact that transition tumour forms exist between these various types; it is certain, however, that there are cases in which adamantinomata demonstrate many of the histological characteristics of the first group; similarly certain other tumours which in the main conform to the features of the squamous papillary cysts, contain here and there areas in which the basal or peripheral cell layers resemble ameloblasts. Cases 3 and 4 in our series are examples of the former variety.

Fig. 9 illustrates a section of a tumour belonging to the class of squamous papillary cyst (Duffy's Group 1). The main features by which it can be differentiated from the adamantinomata are:

(1) The basal membrane is composed of stratified epithelial cells arranged several layers deep.

(2) There is no intermediate zone.

(3) The cells constituting the inner mass differ from the stellate cells of the adamantinomata in being larger, more widely separated, more evenly circular, and less distorted in outline; the nuclei stain only faintly, and there is no intercellular bridging.

(4) There is no tendency for a whorled arrangement of the epithelial cells, and "cell nests" are absent.

(5) The stroma is hyaline in appearance, and is arranged within the epithelial processes so as to form cyst-like cavities.

(6) Cysts of hydropic or degenerative origin are much less common.

(7) There is much less tendency towards necrotic change in the epithelium with resulting keratinization and calcification.

The cells of this type of growth strike one as conforming to an earlier embryonic type of cell, probably corresponding with the primitive ectodermal components of the skin, prior to the formation of the enamel organ. It is feasible, therefore, that such growths may be looked upon as pre-adamantinomata.

Cases 3 and 4 of our series are true adamantinomata in that the basal membrane is typically ameloblastic in appearance and arrangement. The tumour approximates to the squamous papillary cyst type in the character of the inner cell mass. The cells in this region are less definitely stellate in shape, are larger, more widely separated, more

circular, and contain less darkly staining nuclei. There is no intermediate zone. As in squamous tumours, again there is an absence of cell nests, of keratinization, and of calcareous deposition. There is no connective tissue stroma; the colloid cysts rest in a supporting membrane of epithelial cells. These cysts are present in great numbers; they are regular, rounded cavities, containing a homogeneous colloid material. Within this colloid there lie a few sparsely scattered round cells, each one of which is surrounded by a clear area. Similarly

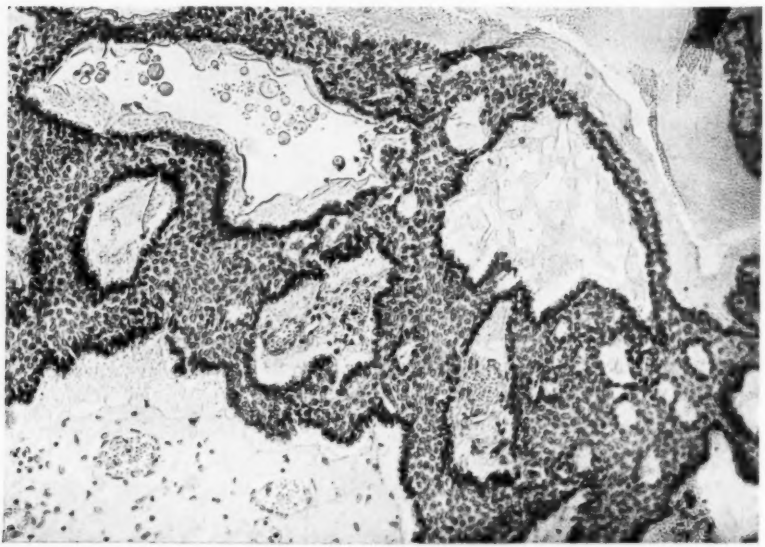

FIG. 10.—Section of tumour from Case 3. The inner cell mass is made up of larger cells somewhat loosely packed. The nuclei are more rounded and stain less darkly than in the majority of adamantinomata and probably represent a more primitive variety. × 150.

Case 4 differs from this type in possessing little or no stroma, the cells of the interior of the epithelial mass do not resemble those in Case 3, but are more elongated, closer packed, and more deeply staining. Such tumours probably belong to a more primitive variety of adamantinoma, and may be regarded as a transition-link between Duffy's group and the common variety (fig. 10).

Differentiation has to be made between the adamantinomata and various other growths in the infundibular region. The chief difficulties arise in distinguishing them from the teratomata, the basal chole-

steatomata, tumours arising from the choroid plexus and ependyma of the third ventricle, the chordomata, the simple cysts of Rathke's pouch, and the cylindromata.

There should be no real difficulty in distinguishing these neoplasms if the essential histological features of the adamantinomata are strictly adhered to. As emphasized previously, the typical adamantinoma comprises a branching trabeculated epithelial mass consisting of an outer ameloblastic layer, a narrow zona intermedia, and an internal mass of stellate cells. Cell nests may appear, and cornification, calcareous deposit, and even ossification are frequent. Cysts containing colloid, mucin, or cholesterin are usually present in large numbers. The whole epithelial structure may be contained within a connective tissue stroma, which varies greatly in amount. There is only one diagnostic criterion, however, and that lies in the demonstration of the peripheral layer of ameloblasts. Usually there is no difficulty in recognizing this layer—the only doubt occurring when the zona intermedia is absent, and the character of the stellate cells is atypical. Cell nests, cornification, calcification, and bone formation are not essential features; nor does their presence prove the tumour to be an adamantinoma. The same statement holds true for the colloid, mucin, and cholesterin cysts, which, though commonly present, may be absent, and also may occur within other epithelial tumours in this region.

In the *teratomata* structures are present which arise from the three embryonic layers—ectoderm, mesoderm, and endoderm. In the adamantinomata the growth is one primarily of ectodermal origin—mesodermal elements serving merely as a supporting stroma. The presence of bone in these tumours has already been explained as resulting from a specialized tissue reaction influenced by the proximity of calcium salts. This process is in no way comparable to the occurrence of bone in the teratoma. Other specialized tissues, such as mature teeth, hair or muscle fibres, serve when present to distinguish the teratoma from the adamantinomata.

Basal cholesteatomata resemble these tumours in containing free cholesterin crystals within an epithelial structure. The cell elements, however, differ in consisting of stratified epithelium and in resembling closely the skin. Erdheim at one time held that the presence of keratohyalin granules favoured the diagnosis of cholesteatoma, but it is now quite certain that these granules do occur in the adamantinomata. There are no cells present which in any way recall the structure of the enamel organ.

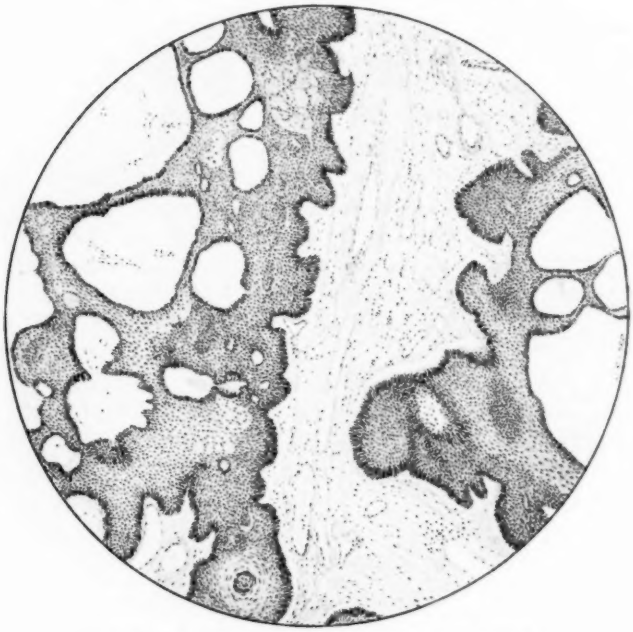

FIG. 11.—Low-power drawing of tumour from Case 5.

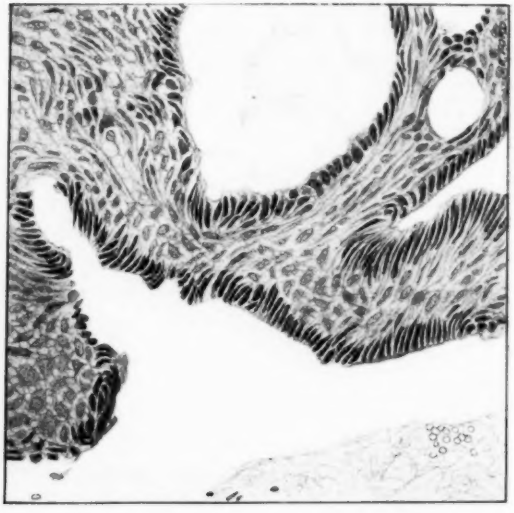

FIG. 12.—High-power drawing of tumour from Case 5, showing the typical ameloblast layer.

The *chordomata* (Burrow and Stewart, Alizais and Peyron) may present a difficulty in differential diagnosis when they arise from the basi-sphenoid bone. The histological appearance, however, is characteristic—consisting in large solid masses of cells associated with a great deal of intra- and extracellular mucin deposition; the cell outlines may become faint so that syncytium-like areas result. There are no columnar cells which bear any resemblance to the ameloblasts.

The simple cysts of Rathke's pouch, arising from a dilatation of the original cavity, naturally compress the pars anterior of the pituitary in a forward direction, and the intermediate and nervous parts posteriorly. The cells lining the cyst wall may be ciliated; the contents are variable, being serous or gelatinous, frequently stained a chocolate colour by reason of altered blood. There are no interlacing epithelial trabeculæ; cell nests, keratinization, calcification, and other retrograde changes are usually absent. Lastly, there is no trace of the characteristic ameloblast layer.

Tumours of the choroid plexus present a very real difficulty in differentiation; it is almost certain that much confusion has arisen in respect to these two neoplasms, and cases reported as choroid plexus tumours have actually been adamantinomata. Two main varieties may be described—*the papillary adeno-carcinomata* (papilloma choroideum of Davis and Cushing), and the *squamous-celled carcinomata*. The former variety is characterized by a scanty connective tissue which usually shows evidence of mucoid degeneration. This stroma carries an abundance of thin-walled varicose capillary blood-vessels, which may actually present an angeioma-like picture. Calcification may be found in the vessel walls. The epithelial elements usually consist in two or more rows of small, delicate cells, the outermost being cylindrical and the inner ones being cubical in form. In the squamous variety epithelial cell nests may appear, and keratinization is not uncommon. The most important diagnostic point lies in the absence of the characteristic ameloblast layer.

Ependymal tumours of the third ventricle are again not easy to differentiate from the adamantinomata. Three types are described:—

(*a*) *The ependymoblastomata* (Bailey).—The histological picture of these tumours consists in small vascular channels surrounded by closely-packed nuclei, the tails of the cells being directed towards the capillary. Blepharoplasten occurs in the cytoplasm.

(*b*) *The ependymomata*: In these growths the stroma is abundant; the cells are polygonal and tailless, but contain blepharoplasten.

(*c*) *The neuro-epitheliomata* (syn. spongioneuroblastom of Ribbert; neuro-epithelioma gliomatosum microcysticum of Rosenthal; blastoma ependymale of Marburg). These growths consist in alveolar groups of cubical or cylindrical neural epithelial cells arranged so as to form ill-defined tubules, or else arranged around capillary vessels. The stroma is composed of glial tissue. Rosette-like figures are produced by accumulations of primitive spongioblasts.

The medullo-epitheliomata have been described growing in the neighbourhood of the infundibulum (Cushing and Bailey), and their histological appearance might conceivably be confused with the adamantinomata. There is an absence of any connective tissue elements, however, between the epithelial masses, which appear to radiate from the numerous small vascular sinuses.

True pituitary adamantinomata have been diagnosed as *cylindromata* of the infundibular regions, the histological appearances being very alike in the two cases. The cylindromata (myxo-endotheliomata), however, are formed of masses of cubical epithelium, uniform in cell structure throughout their breadth. There is therefore no basal (peripheral) layer comparable to the ameloblastic zone. The hyaline products of degeneration differ chemically from those of the adamantinomata, comprising mainly mucin and collagen.

The colloid or "ball" cysts of the third ventricle present a macroscopic appearance which might be mistaken for an adamantinoma of the pituitary. They are spherical, unilocular cystic tumours of a greenish colour and consist in a homogeneous mass of colloid, loosely surrounded by a very thin fibrous tissue capsule. Here and there a few small round cells have migrated into the capsule. There is no real histological similarity between these tumours and the adamantinomata.

The origin of the pituitary adamantinomata is unquestionably from ectodermal tissue, since the only mesothelial elements present serve merely as a supporting stroma, which indeed may be absent. Erdheim's theory of origin from unobliterated portions of the canalis craniopharyngeus has never been disproved, and is in accordance with all the known facts. The reason for the specialization of the epithelium with the production of ameloblasts is comparable to the development of adamantinomata from other areas of buccal epithelium. Melassez [8], in his classical monograph, has emphasized the rôle played by embryonic inclusions—the *débris épithéliaux paradentaires*—in the production of tumours around the jaws. He has pointed out that in the majority of such tumours—sometimes spoken of as the epithelial odontomes—the

epithelium is of the specialized variety, which corresponds histologically to the ameloblasts of the embryonic enamel organ; in other varieties, the epithelium corresponds more closely with the Malpighian layer of the ectoderm; a few instances are transitional in appearance, the epithelium being ill-defined in type.

According to Bland-Sutton, the adamantinomata of the jaw arise from persisting portions of the epithelium of the enamel organ; Leriche and Cotte trace them to the epithelium of the mouth; other authorities regard them as arising from excessive tooth germs. As Leriche and Cotte have pointed out, these divergent views are all very similar, as the prime origin in all is undoubtedly the embryonic buccal ectoderm. In an histological examination of the epithelial vestiges lying around the distal extremity of the infundibulum in normal subjects, we have encountered here and there little clusters of columnar cells, indistinguishable in appearance from ameloblasts. It seems probable therefore that these columnar *réliques* are the clue to the origin of such specialized forms of tumour as the pituitary adamantinomata.

The histological appearances of the adamantinomata are alike, whether arising from the jaws or in the infundibular regions. Both varieties consist in characteristic epithelial trabeculæ bounded by a basal ameloblastic layer, and lying in a variable amount of connective tissue stroma. In both mucoid, myxomatous and colloid changes occur leading to cyst formation, and there is a similar degree of keratinization and calcification—even going on to actual ossification.

The degree of malignancy and the rate of growth of the pituitary adamantinomata are points concerning which it is very difficult to give a definite opinion. Without doubt both features are variable, depending upon the amount of connective tissue stroma, the degree of epithelial necrosis and mucoid change, and the exact type of epithelial cell present. In the case of the adamantinomata of the jaw growth is excessively slow; according to Moorehead and Dewey, cases have been under observation for thirty-eight years. They expand adjacent bony tissues without invading them; in some instances they have recurred after removal, the recurrences showing less and less of the specific characteristics of the original tumour. They do not form metastases.

The infundibular adamantinomata necessarily show symptoms at an early stage by reason of pressure upon neighbouring structures, and by reason of an increase in the general intracranial tension. The duration and rate of growth is therefore very difficult to assess. Many of the growths are locally malignant in that they invade adjacent tissues,

whether dural, bony, or cerebral; many certainly recur after removal. There never appears, however, to be any formation of metastases.

The Clinical Aspect.

Because of the constancy of their anatomical localization to the anterior wall of the infundibulum and the pars anterior of the pituitary gland, and because of certain peculiarities in their physical and chemical structure, the pituitary admamantinomata are associated with a characteristic group of symptoms. These symptoms may be divided into two groups:—

(*a*) Symptoms due to peculiarities of structure, chemical and physical.

(*b*) Symptoms due to the suprapituitary localization of the growths.

(*a*) *Symptoms due to physical or chemical peculiarities of structure.*—The fact that the adamantinomata are so prone to calcification and to osseous changes is a matter of very great clinical importance, because it is possible in almost every case to demonstrate supra- or intrasellar calcified nodules in radiograms. The rarity of calcified shadows in tumours of other types in this region makes such nodular shadows almost pathognomonic. Out of nine of the proved cases under consideration in this paper of which there are skiagraphic records, six cases showed intra- or suprasellar shadows of calcified areas in the growth. In two of the three cases in which no such shadow was visible considerable calcification was found post mortem which might possibly have been rendered visible during life. In the other case (Case 3) there were no calcareous deposits.

Duffy, basing his opinion on the frequency of the adamantinomatous tumours of this region, considered that "such shadows might be expected to be found in something like one half of all squamous epithelial hypophyseal tumours or, in other words, in the majority of tumours of the adamantinomatous type." Calcification may occur rarely in suprapituitary tumours of other types. In eighteen cases of adenoma of the anterior lobe of the pituitary gland observed by the present writers, no similar shadow was visible in the skiagram.

In Cases 1 and 2 a large rounded shadow was visible just above and behind the pituitary fossa, together with some smaller intrasellar shadows. In Case 5 it was possible at operation to remove the calcareous deposit visible on the skiagram as an irregular and nodular opacity, situated above and to the left of the fossa. In two of Duffy's

cases of adamantinoma, radiography showed in one a suprasellar nodular shadow, with partial destruction of the posterior clinoids, and in the other a calcified area just above the sella, but the sella was of normal size. The radiogram of Warthin's case showed a dense mass about the size of a hazel-nut in the anterior portion of the sella. At autopsy this was found to be due to a hard mass filling the sella and projecting above it. This mass gave a clear ringing sound when struck, and was composed of calcareous, mulberry concretions. The sella was not greatly enlarged. Histologically the tumour was a typical adamantino-carcinoma. It can be seen that the shadow may lie to the right or left of the mid-line, and enlargement of the sella may or may not be present.

Something may be said here regarding the differential diagnosis of these shadows. Such localized calcifications are rare in the neighbourhood of the pituitary fossa. Shadows which we have described above as being so characteristic of the pituitary adamantinomata are situated too far forward to be pineal. Heuer and Dandy [6] have referred to one case of calcified tumour arising from the optic nerve sheath, but here again the position of the shadow will differentiate the condition. The same authors have reported a case of aneurysms of the right and left internal carotid arteries, giving rise to incomplete, ring-like shadows, indicating the periphery of a mass above the sella. Such ring-like shadows are quite unlike the shadows found in any case of tumour.

The frequency of certain toxic symptoms before or after operation seems another characteristic of this group of tumours. Thus, eight hours after the opening of the capsule at operation in Case 1, the patient developed air hunger, hyperpyrexia, restlessness, and delirium, followed by death in twelve hours. The symptoms occurred in three of our five cases at intervals varying from eight hours to three weeks after the opening of the tumour capsule. Death with hyperpyrexia occurred within twelve hours of the opening of the capsule in both of Duffy's cases and in Warthin's. A giant urticarial eruption occurred eight hours after operation in Case 3, and Case 2 gave a history of a severe attack of urticaria nine months after the onset of his illness.

Amongst other toxic symptoms observed before operation we may cite itching and pricking of the skin (Warthin); hot flushes, (Case 2); hyperidrosis, and blistering of the skin (Farnell). The appearance of these toxic symptoms soon after operation would indicate the freeing of some metabolic chemical poison from the interior of the tumour. It has been suggested, but without evidence, that the chemical substance in

question is cholesterin, which exists in the adamantinomata as translucent crystals, lying free in the contents of the cystic cavities. It appears likely, however, that this or some similar substance by its absorption into the circulation, or by its release in large amounts into the subdural space during operation, may be the cause of the toxic symptoms peculiar to this group of tumours.

Examination of the spinal fluid has not been carried out in sufficient number of cases to warrant any definite conclusions. It is noteworthy, however, that a pleocytosis has been found by some observers (Mackay and Bruce, Farnell). In Mackay and Bruce's case the cerebrospinal fluid was highly albuminous and contained an excess of leucocytes, of which the lymphocytes outnumbered the polymorphs by 3 to 1. The fluid however was blood-stained.

(*b*) *Symptoms due to the suprapituitary localization of the growths.*—It has been emphasized earlier in this article that the pituitary adamantinomata take origin either from the anterior surface of the infundibulum, or more rarely from beneath the capsule of the anterior lobe. In the latter case the growth of the tumour is upwards, flattening the pituitary gland, so that all such growths eventually become suprapituitary. With such constancy of anatomical localization it is not surprising that symptomatology is strikingly uniform.

For purposes of comparison eighteen verified cases of adamantinomata have been compared with a similar number of verified cases of adenomata of the anterior lobe of the pituitary gland coming under the observation of the writers at the National Hospital, Queen Square.

Of the general symptoms of intracranial tumour, it is worthy of note that in the *suprapituitary growths* papilloedema was present in eight out of thirteen cases in which the discs had been observed; in the other five cases primary optic atrophy was present. In the *pituitary growths* papilloedema was not observed, but in thirteen cases the discs show early or advanced primary atrophy, and in five cases they were normal.

The suprapituitary adamantinomata were never accompanied by acromegaly or gigantism, whereas acromegaly characterized six of the cases of intrasellar growth. In the adamantinoma the bodily conformation in all but four cases was adipose and infantile. The increase in fatty tissue was most noticeable in the regions of the pelvic and shoulder-girdles, and at the back of the neck. The features tended to be delicate and the hands and feet small with tapering fingers. The secondary sexual characters showed regressive changes and were

PITUITARY ADAMANTINOMATA.

	Sex	Age	Sella turcica	Toxic symptoms	Adiposity	Infantilism	Hirsuties	Drowsiness	Polyuria	Optic discs	Termination
1. Case 1	F.	27	Shadow enlargement	Air hunger	+	+	Scanty	+	*Nil*	P. atrophy	Hyperpyrexia, air hunger and death
2. Case 2	M.	10	Shadow enlargement	Hot flushes, urticaria	+	+	Fine	+	,,	Papillœdema	Hyperpyrexia and death
3. Case 3	F.	35	Enlargement	Urticaria ..	+	Uterus and R. ovary atrophic	Falling	*Nil*	,,	,,	Hyperpyrexia and death
4. Case 4	M.	11	Normal	..	*Nil*	*Nil*	Fine	,,	,,	,,	Hyperpyrexia and death
5. Case 5	M.	16	Shadow enlargement	..	,,	+	Scanty	+	,,	P. atrophy	Hyperpyrexia and death
6. Case 6	F.	24	—	*Nil*	*Nil*	*Nil*	Normal	+	,,	Papillœdema	Death
7. Case 7	M.	60	Enlarged	,,	++	+	Feminine distribn.	*Nil*	,,	P. atrophy	Death
8. Duffy (C_2)	F.	11	Shadow enlargement	..	+	+	Increased	++	,,	Papillœdema	Hyperpyrexia and death
9. Duffy (C_3)	F.	23	Shadow only	..	+	Uterine endothelium atrophic	Sparse	*Nil*	..	,,	Hyperpyrexia and death
10. Warthin	M.	18	Large shadow	Prickly feelings in skin	++	Genitals poorly developed, +	Scanty	+	*Nil*	P. atrophy	Hyperpyrexia and death
11. Babinski-Onanoff	F.	17	—	..	+	Uterus and ovaries atrophied	Scanty	*Nil*	,,	Papillœdema	..
Teutschlaender* ..	F.	57									
12. Farnell	F.	43	..	Hyperidrosis blistering of skin	++	*Nil*	Falling	++	,,	,,	Died of pneumonia
13. Mackay and Bruce	M.	16	..	..	*Nil*	*Nil*	Normal	+	,,	Pale	..
14. Strada	F.	19	..	..	+	..	Scanty	+	,,	Papillœdema	..
15. Erdheim (C_1) ..	F.	20	..	(?)	*Nil*	++ small thyroid and genitalia	(?)	Clinical record imperfect			
16. Erdheim (C_4) ..	M.	21	..	(?)	,,	+	..				
17. Erdheim (C_5) ..	M.	33	..	(?)	..	..	..				
18. Cornil	M.	30	..	*Nil*	+	+	Normal	+	+	P. atrophy	Death

* No clinical data available.

under-developed; the hair was short, silky, and sparse, and in four cases almost absent over the eyebrows, axillæ, and pubes. In women, amenorrhœa was frequently the earliest symptom observed. In one case only (Duffy [2]) was the adiposity associated with an increase in the growth of the hair. The patient was a girl, aged 12; during the past two years, the hair of the head had grown much longer and thicker, and although the menses were still in abeyance, a moderate growth of pubic hair had appeared. Adiposity of this type appeared only four times in the purely intrasellar tumours, and two of the cases showed adiposity in addition to acromegaly.

The following cases of adamantinomata, from literature, show that infantilism may or may not be associated with adiposity, and that frequently macroscopic changes are present in the genitals, and in the glands of internal secretion.

Babinski and Onanoff.—The patient was a girl, aged 17, with marked adiposity and infantilism. She had not menstruated. She complained of headache of thirteen years' duration, and occasional fits. Her memory for some time had been deteriorating. Papillœdema was present. At post-mortem a suprapituitary adamantinoma was found. The uterus and ovaries were infantile like those of a girl from 8 to 10 years.

Erdheim (Case 1).—A female aged 20, without adiposity. Infantile, thin, with dry skin. Strikingly small thyroid gland, narrow aorta, underdeveloped mammæ, and infantile genitals. Hairless pubes.

Warthin.—A boy, aged 18, complaining of failure of vision of two years' duration. One year ago severe headache, followed by convulsions and state of lethargy lasting three weeks. At times he complained of a pricking sensation of the skin. Enormously obese. Height 58·5 in. Weight 128 lb. Genitalia hardly visible. Poorly developed. Right testicle undescended. Drowsy.

The cases of adamantinomata were excessively drowsy, and this appeared to bear no relationship to the degree of adiposity or the amount of hydrocephalus present. In Case 1 the relatives informed us that the patient "sits down to rest her head and five minutes later she is sound asleep." In Case 2 the patient was brought to hospital because of lethargy, which had been present for one week, and stupor of some weeks' duration was present in Case 2 of Duffy's series. In Case 5 of our series the lethargy commenced later and lasted throughout the two and a half months following the second operation. It was noticed that these patients, when roused, could answer questions brightly and intelligently. In Case 1 and in Babinski's and Onanoff's case, failure of memory for recent events was one of the patient's chief complaints.

Farnell's case, a woman, aged 43, showed mental dullness, lack of interest, defective memory, sleepiness, later she asked absurd questions and heard voices, became untidy, dirty, and would lie in bed for weeks on end. At times these symptoms would remit and patient's mentality became clear again.

In none of the cases recorded was there any glycosuria, and in two instances only were blood-sugar estimations carried out. In these (Cases 1 and 5 of our series) the resting blood-sugar lay at a level rather lower than normal. After the administration of 50 grm. of glucose the curve showed a delay both in the rise and in the fall, and in both cases the peak of the curve was lower than normal.

By reason of the position and size of these tumours pressure upon the optic tracts with resulting visual defects was an early and marked symptom. All manner of field defects have been encountered, depending upon the direction and the angle in which the pressure was exerted. Thus bitemporal hemianopias, quadrantic defects, or a homonymous hemianopia may occur either singly or in combination. The relative vulnerability of the macular fibres frequently gives rise to early involvement of central vision, causing a paracentral scotoma. Broadly speaking, adamantinomata which arise from the upper set of epithelial *Anlage* tend to exert pressure on the chiasma from above and behind; in this way the earliest field defects will consist in bilateral lower quadrantic defect with or without a paracentral scotoma. Similarly tumours arising from the lower set of epithelial *Anlage* usually infringe upon the chiasma from below and behind, producing in the early stages a bilateral upper quadrantic defect while the macular fibres tend to escape.

There are two main types of anatomical change in the conformity of the sella turcica. Firstly, the sella may be increased in depth, as in a typical acromegalic skull, but there is always an associated widening of the aperture, due to a splaying out and absorption of the clinoid processes. We believe this is the more common type of change found in adamantinomata coming from the lower epithelial *Anlage*. The second and commoner type of change consists in a flattened sella with marked absorption of the clinoid processes, causing a great widening of the inlet, such as is seen in hydrocephalic skulls. This second type occurs most frequently in adamantinomata growing from the upper epithelial *Anlage*.

In judging the depth of the pituitary fossa one's best guide is the distance between the floor of the fossa and the floor of the sphenoidal sinus, which should usually in the adult measure 1 cm.

The age and sex incidence of our cases may be conveniently summarized in the following table:—

Age	Adamantinoma	Adenoma
0-10 ..	1 ..	0
10-20 ..	7 ..	0
20-30 ..	6 ..	2
30-40 ..	2 ..	4
40-50 ..	1 ..	9
50-60 ..	1 ..	3
Males	8 ..	7
Females	10 ..	11

It is obvious, therefore, that the adamantinomata are to be regarded typically as occurring at the time of puberty or early adolescence.

Recognition of these tumours during life as suprapituitary neoplasms should not be difficult. The typical endocrine disturbances, the evidence of pressure on the chiasma, and the characteristic skiagraphic appearances should establish the regional diagnosis. An accurate histo-diagnosis on clinical grounds, with recognition of the adamantinomatous nature of the tumour, is still a matter of uncertainty. The points which should be stressed are the presence of suprasellar opacities revealed in the radiograms, and the presence of various toxic manifestations, such as urticaria and other skin eruptions. It is possible that a more accurate investigation of suprapituitary tumours will reveal other points of diagnostic importance, both clinical and biochemical. A routine examination of the cerebro-spinal fluid in all suspected tumours in this region may prove of assistance in the differential diagnosis.

The importance of making an accurate diagnosis of the nature of the tumour before operation is evident when one considers the results of operation in these cases. Of the eighteen cases here cited eleven were operated upon. In each instance the outcome was fatal, the longest survival period being six months (Case 5). Such a result stands out in striking contrast to the mortality figures for operation upon other types of suprapituitary and pituitary tumours.

In conclusion, we should like to express our thanks to Dr. Holmes, Dr. Walshe, Dr. Adie, and Mr. Sargent for permission to publish their cases, and to Dr. Greenfield for his untiring interest and helpful criticism.

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VESTIBULAR OR LABYRINTHINE EPIDEMIC ENCEPHALITIS.

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THE passing years have revealed many curious phenomena left as residua by a previous attack of epidemic encephalitis. That these phenomena are neither complications nor sequelæ is emphasized by Hall [28], who points out that many of them may occur early in the disease, or else may not appear until the "chronic" period, when they may present themselves as residua with a definite tendency to be progressive or to recur at varying intervals. Cases with only one or two symptoms are so common that a diagnosis of abortive epidemic encephalitis (*forme fruste*) can often be made with assurance, even when the clinical evidence is paltry, but the circumstantial evidence is abundant. Furthermore, it is now legitimate to assume that a patient presenting a certain symptom or syndrome has had an attack of encephalitis, even if the history of such an attack is negative. It would appear, therefore, that these residua are a definite part and parcel of the infective process, but that their appearance varies, possibly according to the intensity and progress of that process.

The virus of encephalitis does not apparently follow any law of selection in the choice of its victims, but in them it has a marked affinity for certain cranial nerve nuclei and their connections, many of which subserve the various factors in the mechanism of equilibrium, as will be shown later. The phenomena associated with disturbance of the oculo-motor apparatus and the positive and negative motor symptoms do not directly concern us here, but the occurrence of vertigo in the condition with other signs of vestibular disorder has not been thoroughly studied in this country, and it is worthy of consideration, not only from the clinical point of view, but in connection with the known pathology of the disease.

Wimmer [51] has shown that the encephalitic virus, like that of syphilis, may remain active for years, giving rise to an intermittent or recurrent process, which is of a progressive nature. Acute classical signs are often absent and in his opinion only a few cases showing

well-marked post-encephalitic phenomena give a history of typical lethargic encephalitis. An onset which is slow, chronic and insidious must often be looked for. Parkinsonism and other types of chronic encephalitis already show a "considerable symptomatological polymorphism"; and departures from type in the form of symptoms of varying character are frequent, and often completely overshadow the more usual clinical picture. The recognition of such types is important, and in this paper an attempt is made, not primarily to distinguish a definite type, but to demonstrate the importance of a group of cases where the diagnosis might easily be missed, and in the event of any specific treatment being found to extend the benefit of such treatment to similar cases which are not classical in character. The group under review, as will be seen later, has an important bearing on many of the symptoms which are seen in the commoner varieties.

The nomenclature at present in use for the different types of epidemic encephalitis is both varied and confusing, but the classification of McNalty [34] is, perhaps, the most promising and scientifically useful. This classification provides for affections of the brain-stem, bulb, &c., and local lesions of the different cranial nerves.

Walshe [49] has appealed for a classification built up upon an anatomical basis, in order to obviate the confusion which already exists. No further apology is offered here for attempting to describe a type, not as the French have done, from the symptoms displayed, but from the probable anatomical seat of the lesion. An attempt is also made to draw up a simple classification which would include all types of cases of epidemic encephalitis.

Reports of Cases from the Literature.

Describing the 1921 epidemic in Alsace-Lorraine, Barré and Reys[5], of Strasbourg, were impressed by the great number of patients who complained of vertigo, loss of equilibrium and lateropulsion, and in whom these symptoms predominated over the ordinary oculo-motor phenomena, which were often fleeting, and the lethargy, which was often late and inconstant in its appearance. Depending upon the presence or absence of associated symptoms, they distinguished an "associated" form and a "pure" form. The second form constituted 12 per cent. of an observed series of cases of epidemic encephalitis. So important do they consider these labyrinthine phenomena that they regard them as cardinal symptoms, second only in importance to the more common oculo-motor manifestations. They often constituted the whole clinical picture in

the first few days of the illness. In other cases, and these were the most numerous, the labyrinthine symptoms were the most important throughout the disease, and in still other cases they existed alone as an abortive form. These observers think the chief interest lies in the fact that, in most cases, the vertigo persisted after "recovery," and that it may be erroneously diagnosed as due to cerebellar disease, *vertiges d'estomac*, Ménière's disease, or cerebral arterio-sclerosis; or that it may be regarded as neurasthenic or functional.

The pure form is described as follows: The patient, who has been in ordinary health, is suddenly seized with vertiginous sensations without any particular lethargy, abnormal psychical excitement or ocular trouble. These sensations may last for some time, and attacks may occur more or less frequently, being often serious enough to compel the patient to abandon his work. At the time of the attack he may find himself dragged over in a definite direction, or he may walk like a drunken man. He is extremely feeble, and a sensation of weight in the head may make him incapable of doing any sustained mental work. A general feeling of malaise is added and sometimes the patient vomits. All these phenomena are alleviated by rest and silence, and increased by noise, walking, or sudden movement.

Days or weeks later, the more usual or better recognized manifestations of epidemic encephalitis may appear, thus allaying all doubts as to the true nature of the malady. This particular syndrome is found, not only in many cases which later become classical, but also in cases where the ordinary signs and symptoms are absent, so that not only is there constituted a special vertiginous onset, but a sharply defined clinical form of the disease.

Owing to the scanty literature at their disposal no definite opinion is expressed as to the cause of the vertiginous symptoms. These writers believe that they may be due to localized lesions in the labyrinthine connections, and they think that any lesion, however slight, of this very sensitive system may give rise to varied and prominent symptoms.

The evidence they obtained of labyrinthine involvement by means of the caloric and rotary tests showed that such a lesion was much more frequent and much greater than would be suspected from the patient's history, even in response to leading questions. They believe that vestibular phenomena are so frequent that they are worth searching for in every case of encephalitis.

This probability is well illustrated in a lengthy article by an American writer, who, in the course of an otherwise detailed account of the

affections of the cranial nerves in encephalitis lethargica, states that "there was as a rule no deafness, but there were occasionally some auditory phenomena." The vestibular portion of the eighth nerve and its significance are thus clinically ignored.

Barré and Reys classify the various types of the disease in the order of their frequency as follows: Ocular forms, myoclonic and choreic forms, Parkinsonian forms, labyrinthine forms, meningeal forms, mental forms, Jacksonian forms, paralytic forms and thalamic forms. "Pure" cases of any of these types are comparatively rare; "associated" cases are common.

Discussing the diagnosis of these labyrinthine cases, emphasis is placed upon the importance of the Wassermann reaction and the services of a skilled otologist, in order to exclude other causes. These writers believe that the triad represented by nystagmus, Romberg's sign and the Babinski-Weill phenomenon is important evidence of labyrinthine involvement, especially when associated with vertiginous symptoms. The Babinski-Weill tests are urged by them as being of more practical value than the caloric or rotary tests, which necessitate special apparatus and which yield doubtful results. In conclusion, they point out that varying degrees of Parkinsonism may be present, and if so the diagnosis is not only suggested but confirmed.

This form of epidemic encephalitis has been somewhat unhappily called the "labyrinthine variety," but in this paper an attempt will be made to show, from a survey of the literature and in accordance with the probable anatomical site of the lesion, that the term "vestibular encephalitis" is a more suitable one.

An examination of the literature has revealed a number of cases, some isolated and some in groups, which can conceivably be included under this heading.

The work of Bollack and Hulphen is referred to by L'Hermitte [31]. These investigators endeavoured to determine the modifications presented by the normal vestibulo-ocular reactions in encephalitis. Six cases were examined and in five the nystagmus elicited by mechanical and electric means was modified. It was abolished in three cases and enfeebled in two. A patient was noted with paralysis (? ocular) associated with falling attacks in whom nystagmus was preserved by exciting the horizontal semicircular canals, whilst it was weakened by stimulating the vertical canal. Further reference will be made to Bollack's work.

In a series of fifteen cases Mackenzie [33] found giddiness in five,

and "revolving on the longitudinal axis of the body" in three cases. Signs and symptoms referable to nuclear centres in close proximity to the vestibular nucleus were noted.

This observer has no doubt that in the acute phase of encephalitis the nervous structures which subserve the function of equilibrium are affected and this affection finds expression by means of diplopia, squint, nystagmus, giddiness, rotary movements, &c. The receptor organ, the labyrinth, is not affected, so "the disturbance must be relegated to the nuclei in the pons and medulla, which subserve the peripheral apparatus." In his experience there is plentiful evidence to show that changes actually do occur in these nuclei, especially in the vestibular nucleus, with or without lesions elsewhere. If ear and cerebellar disease can be excluded, the condition can be described as "a disorder in expression on the part of the proprio-receptive system which is represented in the vestibular nuclei," with or without associated disorders of neighbouring nuclei. Mackenzie also believes that the vestibular nuclei may become the foci of irritation or sites of abnormal reaction for stimuli which impinge on them, not from the vestibular apparatus itself, but from sources of central origin. He finally suggests that abnormal irritation of the vestibular nuclei and their associated structures is responsible for the pathological features of the Parkinsonian syndrome.

Skversy [44] reports amongst a series of cases an onset with headache, vertigo and gradual closure of the eyes. When turning the patient had "a tendency to sway and fall in all directions." Insomnia and Parkinsonism developed later. Another patient showed the illness with a sudden onset, associated with headache, vomiting, dizziness, falling and unconsciousness. An otologist reported that the labyrinths were normal, but on bending forward the patient became dizzy. The gait was very unsteady, and as there was marked ataxia in the pointing tests, Rombergism, intention tremor and adiadokokinesia, the case was thought to be due to a cerebellar lesion. A third patient complained of headache, dizziness, and urgent and difficult micturition. There was definite lateral nystagmus in both directions, a complete left-sided facial palsy and measured and nasal speech; tremor developed later. The symptoms gradually cleared and six weeks after the patient's admission to hospital the condition resembled a multiple sclerosis. A fourth case was admitted to hospital with a diagnosis of acute right otitis media and a mastoid operation was performed. Later the patient developed, amongst other symptoms of encephalitis, headache, diplopia and dizzi-

ness, with a tendency to fall to the right and forwards. Romberg's sign was positive and there was rotary nystagmus to the right.

The case of a child is described by Lewis, King and Dinegar [30]. There was marked nystagmus in both eyes, no strabismus, no ptosis, no diplopia, but Rombergism was strongly positive. Another child had diplopia, headache and dizziness and, when walking, he stumbled into objects. There was no nystagmus; Rombergism is not mentioned in connection with this case.

Amongst the many cases described by Wimmer [51] the following may be quoted as displaying vestibular symptoms. His Case 41 showed an atypical onset, with frequent attacks of vertigo followed by muscular twitchings and obesity. Improvement was noted on treatment with luminal. Case 42 had frequent headaches, giddiness, disturbed sleep, ptosis and myoclonus. Case 43 showed a reeling gait, slight nystagmus in extreme side positions, but no Rombergism. Attacks of giddiness were frequent in Case 46, and there was a reeling gait and a tendency to fall backwards. Nystagmus was absent.

Six cases under my own care are described below, and these are followed by the reports of four cases seen through the kindness of Dr. Hall, of Sheffield.

Similar cases are described by Semmerling [43], Reinhart [39], Neve [36], Achard [1], Achard and Leblanc [2], Cawadias [13], Souques and Alajouanine [45], Bosman [8], Cadwalader [10], Calwell [11], Globus and Strauss [23], Chambers [14], Gross [26], Gilpin [21], Barker, Cross and Irwin [4], Dunn and Heagey [17], Miner and Freeman [35], Jacobsen [29], Perret [37], Grossman [27], and Spinnhirny and Reys [46].

The cases referred to above have been selected from the literature because they show symptoms due to interference with the function of the vestibular apparatus. It will be noted that such symptoms may occur at the onset, during the acute stage of the disease, or later as residua. Other symptoms mentioned, such as vomiting, oculo-motor paralysis, facial paralysis, &c., point to abnormal function of the different nuclei adjacent to or connected with the vestibular nuclei. The special symptoms due to interference with the vestibular nucleus will be dealt with in more detail at a later stage. An account will now be given of epidemics which have occurred, apparently simultaneously, in France and Japan, and which from their nature strongly suggest an infective encephalitis affecting the structures situated around the site of the vestibular centres.

Historical.

A lengthy and interesting account is given by Gerlier [19] of an "epidemic of paralysing vertigo" which occurred near Geneva in 1886. As this and other records appear to have escaped attention by modern writers, and as the symptomatology is so suggestive of what we now call epidemic encephalitis, a lengthy summary deserves inclusion here.

The condition occurred amongst farmers and their labourers in seven different villages in the Canton of Geneva. The ages of the patients varied from 18 to 55. Gerlier saw ten cases in one year, but believed that these did not represent one-quarter of the actual number. The inhabitants were in great fear of contracting the malady, which they dubbed *le tourniquet* (the roundabout).

The chief symptoms were disorder of equilibrium, cervical pains, muscular relaxation and paralysis and ocular troubles. Vertigo was intermittent and came on in attacks. It was accompanied by pains in the neck and back, obscuring of vision, drooping of the eyelids and flexion of the limbs, so that the patient could scarcely stand up, and in fact, often fell. The gait was drunken and, owing to the interference with vision and the drooping eyelids, the patient was compelled to feel his way, reminding one strongly of a drunken blind man, an appearance which enabled this observer to make a diagnosis from a distance of twenty paces on more than one occasion. After the space of a few minutes the patient became normal. Sometimes he could only avoid falling by sitting or lying down. As a rule the attacks were so severe and sudden that out-of-door work had to be abandoned.

Stiffness and pain in the neck, radiating to the shoulders, were common. The head was often pressed downwards and forwards on the chest, and the patient was unable to raise it. That the pains were not muscular was shown by the fact that ordinary movements of the head were not painful, and no tender spots were found over the vertebral column.

As an example of the forms of muscular affection which were noticed may be quoted the case of a man who complained of numbness of one hand, which came on during milking and which disappeared after a short rest, only to reappear on further attempts to complete his task. Definite paralysis occurred in some cases, and stammering and difficulties in mastication in others. One case had difficulty in opening the mouth, and another showed severe dysphagia.

Ptosis was the ocular sign which gave the condition a distinct *cachet d'étrangeté*, indeed, it was of all the signs the most constant in

the series. All degrees were present, and the eyelids were usually unequally affected. Strabismus was not met with, and there was apparently no other ocular paralysis, but the iris reflexes were abnormal and irregular. There were no ophthalmoscopic changes. Subjective eye symptoms were very numerous, especially a clouding of vision during the attack. Patients often complained of double vision, flashes of light and other visual phenomena, and in one patient an attack could be precipitated by looking at a bright light.

The attacks were brief, not exceeding ten minutes in duration. They were duplicated in a less intense fashion, if the patient did not rest after them. Incomplete attacks in the form of tingling of the fingers, shooting pains in the neck, &c., alternated with typical attacks. It was noticed that repetition of certain muscular movements produced paresis or paralysis, e.g., walking produced paralysis of the leg, conversation produced stammering, and mastication was followed in one case by inability to open the mouth. A complete attack often followed on these events, and after it the full function of the affected part was restored.

Between attacks there was nothing to show that the patient did not enjoy perfect health, except in some cases there was slight ptosis, tremor or neuritic pains. The eyes often looked half-shut, thereby presenting what was thought to be a *facies*. Blinking was often marked. The clinical examination of the nervous and other systems revealed nothing else abnormal.

Change of air stopped the attacks, which were usually diurnal and never occurred in bed. Rest was always a sure remedy. *La malade qui garde la chambre immobile n'a rien à craindre de l'accès.* Fatigue, noise and traffic on the other hand, or even a strenuous movement, usually precipitated attacks. The cowherd could milk in the morning but he could not milk at night.

Repeated and regular contractions of groups of muscles were noted, and occurred during the acts of milking, sewing, pumping and walking.

The number of attacks gradually lessened in number, became incomplete, and after a time they almost disappeared. Believing that the hot season had something to do with the outbreak, Gerlier promised complete cure when winter came. A footnote, added in the December following, intimates that all the patients had resumed work and were almost cured.

No evidence of lathyrism or other food-poisoning could be found, and alcohol as a cause was excluded, although the frequency of attacks

on Mondays showed that alcohol and especially absinthe precipitated them. Anger and excitement were also possible exciting causes, but most of the patients were of a stolid nature. An "incomprehensible phenomenon" was the fact that women, on the whole, were spared, so that the possibility of the condition being hysterical was minimized. Direct infection was often evident, and six instances were given.

Gerlier concluded that the symptoms were reflex phenomena. "It is a morbid state of the centre of innervation and not a pathological state of the muscle-fibre." The affection, in his opinion, acted principally upon the motor cortex where it seemed to have a selective action on certain nerve filaments, such as those passing to the extensors of the head, the extensors of the fingers and the muscles of the eyelids and jaws. "By fatigue the patient loses the benefit of his environment; he enters into a phase of unstable equilibrium when the simplest cause, the slightest encouragement, a look or a movement of the head suffices to provoke an attack."

In 1888 he distinguished three types of attack [33] :—

(1) *L'aveugle ivre*, "the drunken blind man," already described. (2) *Le recueillement*, "meditation," where the patient suddenly stands still and immovable, with his head inclined upon his chest awaiting the end of the attack, the whole attitude resembling that of the peasants in Millet's well known picture, "The Angelus." (3) *L'homme qui dort debout*, "the man who sleeps on his feet." This is the slightest form of attack, where the eyes are simply closed by ptosis.

Cases were reported by other observers for some years and relapses were frequent. In 1895 the malady appeared to have become extinct, only to reappear in 1896.

In Japan, in 1887, Nakano saw 283 patients, seventy-eight of whom were women, who were affected by what is known as *kubisagari*, "he who hangs the head." These cases were fully investigated by Miura, a former pupil of Charcot's, who promptly recognized the resemblance to Gerlier's disease. In an able review of Miura's work Couchoud [15] enumerates the former's opinions, which were that *kubisagari* was a disease endemic in a certain part of northern Japan, where it appeared almost exclusively during the warm season. It manifested itself by short and irregular attacks which were nearly always provoked by fatigue. These attacks were characterized by a sudden muscular weakness affecting primarily the ocular muscles and producing ptosis, diplopia, &c. Paresis of the neck muscles gave the malady its name. Paresis of the muscles of the tongue and lips, and

more rarely of the trunk and limbs, also occurred. Between attacks there sometimes persisted a certain degree of ptosis, weakness of the neck muscles and exaggeration of the tendon reflexes. Miura found that in the affected area it was usual to have the house so arranged that a part was used as a stable, while the family occupied the remainder of the building, and he agreed with Gerlier's suggestion that stables were the sources of infection. The seasonal incidence of the condition was ascribed to the hardships and exposure incurred by the country people in the spring and early summer as compared with the more restful winter. The rôle played by absinthe as an exciting cause in Switzerland was ascribed in Japan to *mochigome*, a very indigestible glutinous cake which was popular at the village feasts; attacks were always more frequent after such festivals. Miura did not however accept the term "vertigo" as a name for the condition, as this symptom was not so prominent in his experience as it was in Gerlier's earlier cases.

Cases were reported from time to time up to 1912, and in that year Couchoud went to Japan and conducted a lengthy clinical investigation into the condition. He described some thirty-two cases and confirmed the clinical experiences of Gerlier and Miura. He emphasized the distinction between slight and severe attacks; only the severe attacks showed the marked muscular paresis which permits a certain diagnosis. The painful phenomena described by Gerlier were seldom found, and vertiginous phenomena were absent. In his opinion paresis of the muscles of the jaw merits a foremost place in the clinical picture. His facts seem to establish that the condition may exist in a latent manner, and that it may occur during the winter. Between attacks there were no constant stigmata except ptosis, drooping of the lower lip and exaggeration of the tendon reflexes.

Couchoud claims to have isolated a Gram-negative staphylococcus which, when successfully injected into cats, produced symptoms of *kubisagari*, such as transient paralysis of the extensor muscles of the neck and limbs and of the muscles of mastication, and drooping of the eyelids. There was no pyrexia or anorexia, and complete recovery usually followed in a few days.

On analysis the reports of these obscure epidemics cannot fail to recall the features of the recent visitations. In Gerlier's cases we find ocular phenomena in the form of ptosis, diplopia and abnormal pupillary reflexes; muscular phenomena in the form of paresis, paralysis and myoclonus; tremor; a stolidity which strongly suggests Parkinsonism;

pains of a polyneuritic nature—a changing and fulminating clinical picture, surmounted by an extraordinary vertigo. In the Japanese cases ptosis, muscular weakness and exaggerated tendon reflexes were more prominent. The two groups of cases have much in common, and there seems to be little doubt that Gerlier's disease and *kubisagari* are variants of the same condition. There can be no doubt that they are due to an infective encephalitis which has occurred in epidemic proportions in two widely separated parts of the globe. According to Couchoud the condition still occurred in Japan in 1912. Four years later the first cases of epidemic encephalitis were discovered in Europe, during a time when men were migrating in hundreds of thousands across the face of the earth.

An interesting point in epidemiology now arises. Did the pandemic of the last decade arise from the endemic *kubisagari* of Japan or possibly from undiagnosed or wrongly diagnosed cases of Gerlier's disease in Europe, and did the movements of troops to and from all the ends of the earth and across the seven seas provide the necessary mode of transmission to subjects rendered suitable by the hardship, fatigue and semi-starvation of war? An answer in a paper of this kind is not possible, but the evidence is certainly suggestive.

Pathology of Epidemic Encephalitis.

An extensive literature has already appeared concerning the pathology of this infection, and on the whole there is marked agreement in all quarters, not only as to the nature of the lesion, but also as to the sites. Lesions affecting the meninges and lesions affecting the spinal cord and peripheral nerves are described, but between these two extremes the majority of reports show that the basal ganglia, midbrain, pons and medulla are the regions more frequently attacked.

The topographical distribution of the lesions in a case described by Schaller and Oliver [41] is of interest. The illness had commenced with a severe attack of lethargic encephalitis, with tinnitus, occipital headache, abdominal pain and convulsions. The condition recurred more than a year afterwards with difficulty in speaking and swallowing, headache and generalized pains. There are spontaneous past-pointing to the right, and a " perverted " nystagmus occurred when the left semicircular canal was calorically stimulated. Romberg's sign was negative and the gait was normal. The reflexes were hyperactive and tremors and twitchings were present. Localized pain and spasm of the abdominal muscles led to an exploratory laparotomy being made, but nothing morbid

was found. The patient died from bulbar paralysis. At autopsy, typical chronic lesions were found in the nucleus ambiguus, and the inferior olivary nucleus showed degenerated cells. The hypoglossal nerve and its nucleus were normal. The cells of the nucleus of the glossopharyngeal nerve, and of the dorsal and ventral cochlear nuclei, all showed shrinkage and nuclear eccentricity. The root of the acoustic nerve contained a large perivascular hæmorrhage. Lesions were also present in the motor nucleus of the trigeminal nerve and in the superior vestibular nucleus. The nucleus of the trochlear nerve showed a mixture of normal and abnormal ganglion cells, whilst the oculo-motor nucleus, the substantia nigra and the red nucleus were all normal. Slight lesions were found in the putamen, globus pallidus and caudate nucleus, but none were present in the cerebellum or cerebral cortex.

It will thus be seen that lesions may occur in the region of the vestibular nucleus, in the nucleus itself, or in the nuclei connected to it by means of the medial longitudinal bundle. Furthermore, the globus pallidus, which is stated to have a direct connection with the vestibular nucleus, appears to be one of the commonest sites for the lesion of chronic or progressive epidemic encephalitis. In this manner many of the vestibular reflex arcs are liable to interruption, and the removal of the controlling influence over equlibrium which the globus pallidus might conceivably exert through the vestibular nucleus will render this nucleus and the receptors of the vestibular nerve hypersensitive, or the control may become exaggerated and these structures may become less responsive. Lesions of the cerebellum, except in the dentate nucleus, appear to be rare, and cases with cerebellar symptoms are described where no changes in this structure were found at autopsy. The most plausible explanation of such phenomena is that the cerebellar control was interfered with owing to a lesion of one or more of the vestibular reflex arcs.

Experimental Encephalitis.

The work of Szymanowski and Zylberlast-Zand [47] is of special interest in connection with the subject of vestibular encephalitis.

The results of their experiments cannot be quoted in detail, but the following examples are chosen. After inoculation with idiopathic herpes, rabbit No. 1 in running "deviated towards the right, fell on its flank and rotated on its longitudinal axis," and when placed upon its legs (? hind) there was vertical nystagmus. Rabbit No. 4 showed circus movements. A number of rabbits were inoculated with the virus of

encephalitis obtained from infective cerebro-spinal fluid, nasopharyngeal washings and brain emulsions from humans dead from the disease. Rabbit 21A, so inoculated, developed circus movements and when running "it failed to avoid obstacles and often hurt its muzzle against the wall." Other animals were inoculated with brain emulsions from animals already infected. Rabbit No. 31, thus treated, "when put on its legs executed definite circus movements; it frequently rotated on its longitudinal axis, the right side turning round to the left," and "there was vertical nystagmus, more marked in the right eye." The most common symptoms noted were abnormal positions of the head, circus movements, nystagmus and oscillatory movements of the head, all signs of labyrinthine or vestibular involvement. Reference is made to an article by Siegrist and Stocker, who in fact observed involvement of the labyrinth and thought that this was the cause of the symptoms. The work of Doerr and Schnabel is also mentioned, as they found the same symptoms in animals. In the series of experiments under review, no involvement of the labyrinth was found and the phenomena are attributed to involvement of the nervous system and the changes described below are capable of explaining them.

In the acute forms of the experimental disease infiltration was found in the lenticular and caudate nuclei, but no lesions in the cerebellum, pons or medulla. In one rabbit chromatolysis was marked in the nuclei in the floor of the fourth ventricle and Deiters' nucleus showed extensive cellular disintegration. In the chronic form rabbit No. 31 "helped to determine the origin of the labyrinthine symptoms." No changes were found in the brain except in the vestibular nucleus and in the tuberculum acousticum; the cells of the vestibular nucleus were degenerated. Slight changes were present in the cells of the other nuclei of the floor of the fourth ventricle, but the cells of the cerebellum, the red nucleus and the dentate nucleus were not affected.

Reasons are offered why these animals so often developed circus movements and disturbances of static position, which these investigators believed never to occur in man. They suggested that the virus has a selective affinity for the vestibular nerves in animals, as it has for the oculomotor nerves in men, or that it may be due to some special arrangement of the blood-vessels or some biochemical properties of these nuclei. In view of contentions which are quoted below, it is necessary to note that all the animals infected with either virus showed inflammatory changes in the liver similar to those described in man, and none in the spleen and kidneys.

The conflicting results obtained by other observers led McCartney [38] to suspect the animals used, and his findings have gone a long way in shaking the confidence which has been placed upon the results of experimental investigation. He examined the brains of 372 rabbits, some of which were healthy and others of which were being used for experimental work in other directions. He noted that, in many animals, lesions were present which could be mistaken for those of encephalitis, e.g., perivascular infiltration, meningeal involvement, &c. In rabbits "sick" with snuffles, pneumonia, septicæmia and subcutaneous abscesses, the number presenting these lesions varied from 70 to 76 per cent. Attempts to transfer the lesions to other rabbits failed. It is concluded by this investigator, that the "accidental" cerebral lesion in the rabbit is of a wide variety and of so frequent occurrence as to be regarded as existing before any experimental procedure. The recognition of this possibility is most important before any conclusions can be made, which are based upon similar changes in these animals.

Da Fano [16] agrees with these observations and believes that this "spontaneous" form of encephalitis or encephalomyelitis may occasionally occur in circumscribed epizootics. He further states that it is associated with renal lesions, and a sporozoon has been detected in the brain and renal lesions.

It will therefore be seen that experimental medicine is not so helpful in this condition as it has been in others. It is difficult to discard the work of Levaditi, but as the identity of his original virus has been challenged and, as other competent observers have failed when working along similar lines, his findings, for the present at any rate, must be carefully accepted. The results of the work of Szymanowski and his colleague stand the test on at least two counts, viz., (1) their cases showed no renal lesions, and (2) they were able to transfer the condition to other rabbits. Moreover, they did not confine themselves to experiments with a single virus, and they discarded a large number of animals which showed signs of secondary infection by pasteurella. Their findings make an important contribution towards the establishment of a vestibular lesion in epidemic encephalitis.

Symptomatology.

Nystagmus.

Variations in experimental nystagmus in epidemic encephalitis have been investigated by several continental authors, but the only reference found in our language is that of Mackenzie [33], who noted that the

reactions were exalted in some cases during the acute phase, producing such symptoms as giddiness, vomiting and nystagmus which was sometimes spontaneous in a particular posture, and disappeared when the posture was changed. There was no affection of hearing.

Twenty-four cases, all of whom complained of diplopia, were examined by Bollack [7]. A sixth-nerve paralysis was noted only in one case, and a partial paralysis of the third nerve in another. In nine cases the ocular movements were normal, and the remainder presented disorders of associated movement, such as convergence, &c. Nystagmiform jerkings of a surprising violence occurred in twenty-one cases. The nystagmus was of an oscillatory and variable type, occurring in extreme positions, and in this writer's opinion it constituted an important diagnostic sign. Vestibular nystagmus was investigated in seven cases. It was only normal once, and in general it was weakened; it was concluded that in encephalitis there is a true systematization in the lesions of the vestibular tracts and their connections.

Grahe [24] quotes the investigations of Gross, who found irritability of the vestibular organ in three cases during the acute phase of the illness. Two of these cases later became hyposensitive and the third was normal. Grahe himself examined the cochlear and vestibular functions in twenty cases, which varied in character clinically from the typical lethargic case to patients who appeared cured. All degrees of disturbance of the auditory and labyrinthine organs were found, of no definite type and exhibiting variations from time to time, even in the same patient. Actual damage to the sense of hearing was rare, but tinnitus was present in one case. Any difficulty in hearing which was present could be relegated to the cochlea by means of the tuning-fork test. Only one patient complained of vertigo and vomiting, but spontaneous nystagmus existed in thirteen cases; it was either horizontal or rotary in type, and no cases with vertical nystagmus were seen. In nine cases it varied from day to day, and it was constant in only four cases. A similar variability was present in past-pointing. In ten cases, tested at different times, the results varied and there was no relationship between the direction of the past-pointing and the direction or intensity of the nystagmus. Romberg's sign was looked for in too few cases to give any definite data. The caloric test showed that in all but six cases there was a varying sensibility in each side, and a hypersensitiveness was often marked. The rotary test, employed in two cases, gave normal results, and galvanic hypersensitiveness was found in those cases where caloric hypersensitiveness existed.

The findings of Gross were not confirmed; both hypo- and hypersensitivensss of the vestibular organ were found with no regularity and with great individual variation. The author concluded that as the peripheral changes were so very variable we must seek an explanation in central changes.

In a more recent paper the subject is dealt with by Fischer [18], who also describes a paroxysmal spasmodic rolling of the eyeballs in an upward direction, which he has noted in five cases, the eyes staying in that position for hours or even days together, and often giving rise to severe pain. A spontaneous vertical nystagmus was often observed, accompanied by clonic spasm of the upper lids. In his experience spontaneous nystagmus is present in 50 per cent. of chronic encephalitic cases. Vestibular reactions were examined in twenty patients, three of whom showed complete immobility of the eyeballs. Five had the "spasmodic cramp of the upward glance" described already, and the others showed jerking and protracted eye movements in the vertical and horizontal directions. Spontaneous nystagmus was, of course, absent in those cases with complete external ophthalmoplegia. In the "spasmodic cramp" cases there was a slight spontaneous vertical nystagmus on looking upwards, and this was increased during an attack. The other cases showed a horizontal rotary nystagmus, which changed from time to time in its intensity. The vestibular function was tested by the caloric method, and in those cases where paralysis prevented the eye being moved upwards the rotary test was employed. The results were as follows: In the cases with rigid eyeballs, syringing of the ear not only produced nystagmus, but the patients were able to move their eyes about at their own free will for some ten minutes. In the cases with fourth-nerve paralysis nystagmus was again produced and again a temporary cessation of the paralysis occurred. In some of the other cases a typical experimental nystagmus was produced by the caloric method, the direction being horizontal and rotary. Sensations of giddiness and malaise occurred only in two cases.

The conclusions drawn are important and suggest that disturbances of the eye-muscles are not directly due to any disease of the oculomotor nuclei, but to some supranuclear lesion. Grahe believed that these findings confirmed up to a point the existence of the connections which pass between the globus pallidus and the vestibular nucleus.

These findings were previously suggested by Sauvineau [40], who laid stress upon the presence, in encephalitis, of a bilateral

nystagmus due to an irritative lesion of the centres which preside over these movements. If such a lesion were destructive nystagmus would cease and complete ophthalmoplegia would occur. He found no case with evidence of lesions affecting primarily the nuclei of origin of the oculo-motor nerves, and as no systematic lesion existed clinically he decided that the ophthalmoplegias were due to supranuclear lesions, probably in the subependymal grey matter of the ventricles, since lesions of nuclei give rise to paralysis of an isolated nerve or one of its branches, whilst supranuclear lesions give rise to paralysis of a function.

In his work already referred to L'Hermitte [31] states that he succeeded in restoring normal nystagmus in a patient who had oculo-motor paralysis, associated with falling attacks, by exciting the horizontal semicircular canal, whilst stimulation of the vertical canal showed only a weak nystagmus. The horizontal canal was stimulated by rotation with the head vertical and the vertical canal by rotation with the patient recumbent.

A case, under the care of Dr. A. J. Hall, was seen by me during an attack of "spasmodic cramp of the upward glance." The patient lay on her right side, and the direction of the eyeballs was upwards and to the left. There was extreme nystagmus, mostly of a vertical character, with tremor of the lids, arms, &c. She was able to fix an object in any direction at will, but was unable to sustain that direction for more than a few seconds, after which the spasm reasserted itself. When turned over on to her back the eyes were found to be directed upwards, but centrally, the other phenomena continuing, and when turned on to her left side the eyes were found to be directed upwards and to the right, the nystagmus, &c., persisting. In other words, change of position changed the direction, but not the character of the phenomenon. This would point to some vestibular excitement, which was influenced by posture or position, and which reacted upon the centres controlling eye movement.

In my own series of cases varying results were found on inducing nystagmus with cold water. Cases 1 and 3 showed no irritability; Case 3 gave a violent reaction in 10 sec., when the right ear was stimulated; Case 4 had hypersensibility on the right side, nystagmus being produced in 23 sec.; Case 5 was hypersensitive on both sides, nystagmus occurring in 27 secs. on the right side, and in 20 sec. on the left, and Case 6 gave reactions which were practically normal. These findings should be contrasted with the results of the Babinski-

Weill reactions (see Appendix) which were conducted on different days in each case.

There is plentiful evidence, therefore, that there exists in epidemic encephalitis not only spontaneous nystagmus, but abnormal induced nystagmus. There is no constant type of abnormality, and none can be expected when the nature of the lesion is remembered. Cases with complete ophthalmoplegia externa are rare, but through the kindness of Dr. Hall a case was examined by me in order to confirm the extraordinary findings described by Fischer. W. W. (Case S. 2) showed in April, 1925, a residual drooping of the right eyelid, and an almost complete ophthalmoplegia. When seen six months afterwards the ptosis was marked on the right side and the patient was unable to move his eyes in any direction. A fine rotary nystagmus, amounting only to a quiver, occurred in attempted movement, but there was no definite movement. He complained of diplopia and wore a shade over the right eye to exclude the weaker image. Both ears were syringed with cold water several times, and the ptosis was relieved and the patient was able to move each eye in every direction. The range of movement was by no means complete, but it was definite. Complete movement could not be expected when it is remembered that the ophthalmoplegia was of at least six months' duration. Marked nystagmus also occurred, and the patient declared that he could see much better as his eyelid was raised and the diplopia had disappeared. As in Fischer's cases the phenomena were only transient. Such findings, however, serve to show that we have evidence not only that a vestibular lesion exists in epidemic encephalitis, causing spontaneous and abnormal induced nystagmus, but that such a lesion can be responsible for the commonest group of symptoms in the condition, namely, the ocular manifestations.

The Babinski-Weill Phenomena.

This series of phenomena, although it has attracted much notice in France, has received no attention in this country. Prolonged search through English medical literature did not yield a single reference, so a somewhat lengthy description will be inserted here.

First described by Babinski and Weill [3], a more detailed account was written later by Weill and Amado [50]. Normally a person is able to walk and maintain his balance without difficulty in the dark, or with his eyes shut. Moreover, it is possible under these condi-

tions to move in a definite direction. These facts form the basis for the series of tests which are described below.

A large room is necessary. The patient stands at one end looking towards an indicated point at the other end. He is then instructed to walk forwards, towards this point, and then to walk backwards without turning, to the point he started from. This walking to and fro is repeated a definite number of times, e.g., five paces each way, repeated six times. The eyes are now blindfolded and the performance is repeated, if possible without hesitation or interruption in exactly the same manner. When the test is complete a patient with normal powers of equilibrium will not have deviated greatly from the original direction. Slight divergence may, however, occur along a line which is taken as the line of terminal orientation. The angle made by this line and the original is normally said to be never more than 45°, and it is usually inconstant in successive tests. Such an angle, however, measures the degree of deviation, and is called the "spontaneous angular deviation," or *déviation spontanée angulaire*. "Induced angular deviation" may be obtained by combining this test with the caloric, rotary and galvanic tests.

If a normal person is seated a galvanic current of 2 or 3 milliamperes passing through his head will cause a movement of rotation or inclination of the head towards the side of the anode or positive pole. Gleason [22] is of the opinion that such electric tests apply only to the auditory nerves and have no bearing on the condition of the labyrinth. The "galvanic angular deviation" is produced as follows: Electrodes are placed above and in front of the tragus. Bristow's soft lead plates were used as electrodes in my own investigations; bent round a piece of rubber tubing they can be easily applied and firmly secured by tying the tubing around the head. Pieces of moist cotton wool were packed between the plates and the skin. Instead of using two separate leads, a long piece (6 yards) of twin-flex was employed, and it was found that when the patient walked up and down this could be easily held out of the way, so that it exerted no pull, such as was found to occur in extreme deviations when two separate leads were used. When the electrodes are in position and the patient is blindfolded, a very small current (1 milliampere) is passed and the test continued as before. An angular deviation, the galvanic angular deviation, will now occur, usually through about 90° in the direction of the anode or positive pole. If the current be now reduced to zero, a "galvanic angular counter-deviation" will occur to the opposite side, bringing the patient back to his original direction.

Several anomalies occur, but in the majority of cases the test is said to be a very delicate one. Absence of galvanic deviation denotes abnormal resistance or hyposensibility of the eighth nerve or its nucleus. As can be imagined, galvanism can either correct or exaggerate the spontaneous deviation.

"Caloric angular deviation" can also be ascertained. It appears very distinctly in normal subjects after brief irrigation with cold water, even before caloric nystagmus is manifest. The deviation is towards the irrigated ear. With hot water the deviation is in the direction opposite to the irrigated ear. A rotary angular deviation is also described.

According to Weill and Amado abnormal galvanic vertigo indicates a disturbance of the vestibular function, even in those cases where the caloric and rotary reflexes seem normal. If unilateral inclination or predominance to one side is present it is usually towards the affected side; in bilateral lesions, towards the most affected side. In the early stages of labyrinthine lesions where there are subjective troubles and perhaps spontaneous nystagmus, galvanic deviation is strongly unilateral, and shows the side affected. In the later stages, when symptoms have disappeared, it is still unilateral, and a more or less marked resistance is often present. Abnormal galvanic vertigo is met with in people who do not show the least ear trouble. Vestibular lesions are exceptional in people showing normal galvanic vertigo or deviation.

In order to carry out these tests I drew up the following routine. The reactions of nine apparently normal persons were investigated as controls, as well as those of ten encephalitic cases, six of whom were under my care. The other four cases were selected for investigation from a number seen at Dr. Hall's clinic. The sole criterion in the selection of these latter cases was spontaneous nystagmus or ophthalmoplegia.

Test 1.—The patient is made to walk five paces forwards in a given direction and five paces backwards without turning. This is repeated six times in order to impress the direction upon the patient's senses. Any abnormality of gait can be noted.

Test 2.—He is now blindfolded, and Test 1 is repeated. The spontaneous angular deviation is now noted, as well as the direction, to the right or the left as the case may be.

Test 3.—The patient, being still blindfolded, a fixed amount (25 c.c.) of cold water is now syringed into the right ear, and the trips forwards and backwards repeated. After making due allowance for the spon-

taneous deviation, the resultant deviation is the caloric angular deviation. The symptoms produced, such as vertigo, nausea, &c., should be noted, as well as the effect upon the gait. (In practice it was found that induced nystagmus had usually ceased by the time the test was completed.)

Test 4.—A rest of about ten minutes should now be allowed, especially if the last test produced severe symptoms. Test 3 is now repeated, this time syringing the cold water into the left ear. The deviation, symptoms, &c., should again be noted.

Test 5.—After another rest the electrodes of the galvanic battery are now attached to the patient's head, with the positive pole to the right. He should be allowed to finish a few trips before the current is switched on, and as there is usually a flash seen by the patient, it is as well to warn him of this. With a current of one milliampere flowing, six excursions, up and down, are made, and the deviation and the symptoms noted. A second flash is seen when the current is switched off, and a counter-deviation to the opposite side may then occur.

Test 6.—Having again allowed a rest, Test 5 is repeated, this time with the positive pole to the left. The results are again noted.

The results of these tests in cases and controls are given in the Appendix (p. 520). Even a glance at these tables will show that the findings in these post-encephalitic cases differ greatly from the normal. Induced deviation may vary from nil to 360°. The direction of the deviation may be normal or abnormal, and the symptoms produced, especially in the cold caloric method, are much more severe than those produced in apparently normal individuals. These findings, of course, need verification, as the number of cases and controls examined is, by force of circumstance, very small. They serve to show, however, that epidemic encephalitis can, and does, leave a derangement of the vestibular paths.

Romberg's sign.—This well-known sign, which is included in the triad of Barré and Reys, needs no description. Its interpretation, however, does not appear to be clearly understood. It simply shows whether or not the posterior columns of the spinal cord are functioning properly, and, if positive, it is a sign that the patient is depending on visual impulses in maintaining equilibrium, and that the sensory paths are interfered with. It is therefore not an indication of vestibular interference, but shows that the sensory impulses from the skin, which are necessary in maintaining equilibrium when the eyes are shut, are not passed.

Hautant's test, or the outstretched arms' test.—The patient is made to sit down, and with his eyes closed to extend his arms and hands, and to keep them parallel in a position in which the observer places them. A normal subject is able to maintain this position for a long time; but if there is any interference with the labyrinthine function, according to Barré and Reys, one or both arms will move slowly, but progressively, to the right or left, through a distance of 10 or 20 cm. It was present in all my cases, but appeared to vary from time to time.

None of these symptoms can be considered diagnostic in themselves, and as the signs are not obvious their presence may easily pass unnoticed. These two factors have probably caused such signs and symptoms to be ignored, except where they were conspicuous.

Reports of Cases.

Case 1.—Miss H., aged 36, a shopkeeper, had an illness in January, 1924, with catarrhal symptoms and severe vertigo. In the following March the vertigo returned, this time with a fair degree of lethargy and neuralgic pains about the head, neck, and shoulders. (At the same time Mrs. O., her assistant, was very ill with diplopia, vertigo, severe headache unrelieved by drugs, and lethargy, which gave way later to insomnia.) There is a family history of nervous disease, one member having died from disseminated sclerosis, and another is said to have paralysis agitans.

Present condition: The patient is well nourished. Her principal complaint is of vertigo, which still recurs from time to time. She has fallen on several occasions and bruised herself, but has not lost consciousness. The attacks are described as if she were thrown or pushed down to the left side. There is occasional headache, but no vomiting. The pupils are equal and normal, but there is slight ptosis on the right side. There is some spontaneous nystagmus, which, along with the ptosis, varies from time to time. The optic nerves appear normal, as do the other cranial nerves. The gait is unaffected and the reflexes are normal, but Romberg's test shows swaying. There is no dysarthria, dysphagia, or myoclonus, and the face is not mask-like. Hautant's test with extended arms shows slight divergence. The cardio-vascular system, the blood-pressure, the lungs, the urine, and the urea concentration test show nothing abnormal. The Wassermann reaction is negative, and a radiogram showed nothing more serious than some pyorrhœa alveolaris. Mr. F. Holt Diggle reported that "there did not appear to be any active lesion of the labyrinths except that the right one was hypersensitive, syringing with cold water producing a violent third degree nystagmus in about ten seconds."

The Babinski-Weill tests give the following results:—

Spontaneous angular deviation: 45° to right.

Caloric angular deviation, cold water to right ear: 90° to left with lateropulsion to left and nystagmus; no vertigo. Cold water to left ear: 90° to left; no lateropulsion or vertigo.

Galvanic angular deviation, positive pole to right: 135° to right; severe vertigo and nystagmus. Positive pole to left: 135° to left; no vertigo; faint nystagmus.

After the galvanic tests the head was inclined slightly to the right. These tests show that there is a lesion of the right vestibular nucleus or nerve. Compared with the normal, the galvanic angular deviation is increased on both sides, and the reaction when stimulated from the right was severe.

Case 2.—Miss W., aged 40, engaged in household duties. The previous and family history are unimportant. In April, 1923, the patient had an illness, when she "slept like a stone, but sheer determination kept her awake." She had vertigo with some ocular phenomena, but no diplopia. The lethargy disappeared after a month or so, but the vertigo has persisted up to the present time. It varies a great deal from day to day, and is greatly increased by worry or fatigue. The patient describes the vertigo as if she were being pushed over, and the direction is not definite. Consciousness is retained.

Present condition.—The patient has lost weight, but is now regaining it. The face presents a certain amount of immobility, but not a definite "mask." The pupils show a varying inequality, but react to light and accommodation. There is no optic neuritis. A fine nystagmus is present on both sides. The left eyelid shows a slight ptosis. The palatal reflex is present and the cranial nerves are normal. The tendon and organic reflexes are normal and there is no paresis or weakness of the limbs, but the patient sometimes complained, in the earlier part of the illness, of stiffness of the legs. This has now passed off. Romberg's sign is present one day and absent another. When there is vertigo, the gait is unsteady, but not ataxic. There is no difficulty in swallowing or speaking, and tremor and myoclonus are absent. Sensation is normal. Headache is a frequent but varying symptom, and the patient has only vomited once in two years, the cause being obviously gastric. The cardio-vascular system is normal with a blood-pressure of 150 mm. Hg. The urine is normal and the urea concentration test shows normally functioning kidneys. The Wassermann reaction is negative and a skiagram of the skull revealed nothing abnormal. The patient states that her memory is failing and that she is often "muddled," while at other times her mind is quite clear. Mr. F. Holt Diggle could find "no evidence of any lesion in either labyrinth to account for the attacks of vertigo," and Mr. G. Jefferson, F.R.C.S., to whom she was referred later, suggested the possibility of a patch of encephalitis causing the trouble.

The Babinski-Weill phenomena were investigated with the following results:—

Spontaneous angular deviation, 60° to right; gait reeling.

Caloric angular deviation, cold water in right ear, no deviation, lateropulsion towards left, patient "felt queer" and had vertigo and nystagmus, vertical and to both sides. Cold water in left ear, 45° degrees to left, then early counter-deviation to right; vertigo and nystagmus.

Galvanic angular deviation positive pole to right, 45° to left; no vertigo, nystagmus. Positive pole to left, no deviation. No inclination of the head.

These tests would indicate that there is a definite hyposensibility of the vestibular apparatus on both sides.

Neither of these cases can be regarded as strictly "pure" examples of the vestibular variety of epidemic encephalitis, as described by Barré and Reys. The only "associated" symptoms, however, are ptosis, headache, and in Case 2 unequal pupils. Their diagnosis will be discussed later.

Case 3.—J. L., aged 53, a colliery under-manager, became ill with pains in his elbows in January, 1924. Ten days afterwards he had a "chill," and further pains which occurred in his arms, chest and back, and which were so severe that he was unable to sleep. He felt very giddy and had to be led about. There was severe occipital headache, which did not yield to drugs, and he had double vision. He became acutely delirious, and his medical attendant had to give him "big doses of strong drugs" to quieten him. His delirium was definitely occupational in character. Later the pains became easier, and he became lethargic, and on many occasions fell asleep during conversation and meals. The right arm and leg developed a continuous tremor, and from time to time the whole left arm would be moved involuntarily. His speech was halting, and he had some difficulty in swallowing. Vertiginous attacks occurred, but they were never so severe that he fell, or had to save himself from falling.

When first seen in January, 1925, he presented a typical Parkinsonian picture, with immobile face, tremor of head, arms and trunk, &c. He then had complete inversion of the sleep rhythm, sleeping all day and "walking the house" during the night. Tremor was marked in the limbs on both sides, especially in the legs whilst seated. It was increased by excitement or interest. There was an unequal bilateral ptosis, which varied from day to day. The pupillary reflexes were normal and there was no oculo-motor paralysis. A fine nystagmus was present on looking towards the left. The optic discs appeared normal. The knee-jerks were brisk, and the other reflexes showed nothing abnormal. The patient still complained of vertigo and "swimminess in the head."

The was no marked abnormality of gait, and Romberg's sign shows a considerable amount of swaying, but no tendency to fall. Past-pointing was absent, but there was a distinct deviation of the outstretched arms when the eyes were shut.

His wife stated that he has changed greatly. He had formerly been stern and particular, but now he is very placid and easily amused. His memory has weakened, but if given sufficient time he remembers most things. His answers and general conversation are rational. He has abandoned his work because he found that he was unable to carry it on, e.g., he would become lost whilst adding up figures, which formerly presented no difficulty.

In this case, Mr. F. Holt Diggle could find "no deafness or vestibular irritability on either side," but the Babinski-Weill reactions carried out later gave the following results:—

(1) Walking backwards and forwards showed slight reeling.

(2) Spontaneous angular deviation—90° to left.

(3) Syringing the right ear with cold water caused a caloric angular deviation of 180° to the right, accompanied by severe vertigo and slight nausea. The tremor of the head was markedly exaggerated by this test, and a coarse, rapid, lateral nystagmus appeared, as well as a very distinct vertical nystagmus.

(4) Syringing the left ear with cold water caused a caloric angular deviation of 90° to the left, with no vertigo or nausea.

(5) Galvanic stimulation with the positive pole to the right caused a galvanic angular deviation through 135° to the right.

(6) Galvanic stimulation with the positive pole to the left caused no deviation and no vertigo.

The probable interpretation of these results is that the right vestibular connections are hypersensitive and the left are hyposensitive.

Case 4.—Mrs. H., aged 37, became ill in June, 1924, when she complained of double vision. She had severe occipital headache and felt very drowsy. On closing her eyes, on account of the diplopia, she experienced severe vertigo. Distressing tinnitus was also present. The lethargy persisted for about a fortnight, and then the sleep became more normal. During this period there was great wasting, and the face became immobile owing to a bilateral facial paresis, which was greater on the right side. Fine tremors developed in the hands, and there were occasional jerky movements in the muscles of the thighs and legs. The pupillary reflexes and optic discs were normal, and there was a well-marked nystagmus to both sides. Bilateral ptosis developed, again being greater on the right side. The reflexes were normal.

After a time the patient regained weight and was decidedly better. The most striking thing noticed on inspection was a curious clonic spasm of the eyelids resembling the action of the nictitating membrane of birds. It was not accompanied by any convulsive state of the iris. This phenomenon caused the patient great inconvenience, but if she desired to look at anything carefully she could control it by the simple device of covering and holding down one eyelid with her hand. The spasm of the other eyelid then ceased. The bilateral ptosis and facial paresis still persist, the former varying greatly from day to day. Rombergism also varies at different times. Hautant's outstretched arms' test shows some deviation. There are no symptoms pointing to cerebellar involvement. The other systems are normal. Headache is often present and attacks of vertigo still occur, with a tendency to fall forwards. Mr. F. Holt Diggle reported that the hearing was normal, while the cold caloric test in the left ear produced " nystagmus in forty-one seconds, with marked reaction," and in the right ear " nystagmus in twenty-three seconds, with marked reaction."

The Babinski-Weill phenomena were observed as follows:—

(1) The gait was normal.

(2) When blindfolded there was a spontaneous angular deviation of 45° to the left and the gait was unsteady.

(3) With cold water in the right ear, the patient felt so dizzy that she was afraid to start; when she did she staggered and would have fallen had she not

been supported. When steadied she swung round through 90° to the right and then immediately started to deviate to the left, passing through an angle of 180°.

(4) Cold water in the left ear again caused severe vertigo and a very unsteady gait, the angular deviation produced being through 360° to the left, in four trips only.

(5) Galvanic stimulation with the positive pole to the right caused a galvanic angular deviation of 45° to the left.

(6) With the positive pole to the left, the deviation was through 135° to the left. After the galvanic tests, the head was inclined to the left.

These phenomena point to both vestibular systems being in a hypersensitive state, with a left-sided predominance.

Case 5.—W. B., aged 62, an electric-tram driver, was driving his car one day in January, 1924, when he saw two trams, side by side, rapidly approaching him. He pulled up and had the presence of mind to shut one eye—and only one tram passed. The experience alarmed him, and as the diplopia continued, he left work and reported sick. The double vision persisted some time and he became lethargic. There was a fluctuating strabismus and some nystagmus. Ptosis developed on the right side and he complained of pain and deafness in the right ear. He had neither tinnitus nor vertigo. Headache, vomiting and delirium were absent. Pyrexia was very slight.

The patient gradually improved, but the lethargy gave way to a modified inversion of the sleep rhythm. He was able to resume work about two months after onset, and had then apparently recovered, apart from the perverted sleep and some ptosis. In January, 1925, twelve months after the onset, he was again seen, and this time he complained of vertiginous attacks in the nature of "swimminess." He had not fallen, but he always liked to have some support when these attacks overtook him. He still had insomnia by night, and during the day he slept whenever he had the opportunity. Ptosis was marked on the right side. The eye movements were normal, with slight nystagmus on looking towards the left. The pupils and optic discs showed no abnormality. On attempting to smile or show his teeth, a fine tremor appeared on both sides of the face, and neither of the actions appeared to be complete. Protrusion of the tongue also showed tremor. There was no difficulty in swallowing, but his speech was deliberate and halting. There was no adiadochokinesis, &c., but there was some past-pointing and deviation with outstretched hands. Rombergism showed slight swaying, but no marked tendency to fall. The usual reflexes showed no departure from the normal. Myoclonus in the form of quivering and jerking of the abdominal wall was complained of. Syringing of the right ear with cold water produced nystagmus in twenty-seven seconds; and with the left ear nystagmus occurred in twenty-three seconds.

The results of the Babinski-Weill tests were as follows:

(1) Walking up and down showed an unsteady gait which was inclined to be festinant.

(2) Spontaneous angular deviation was 90° to the left. The gait was still unsteady.

(3) Cold water in the right ear caused a caloric angular deviation of 360° to the right, with severe vertigo and an increased unsteadiness in walking.

(4) Cold water in the left ear caused a caloric angular deviation through 360° to the left, with slight vertigo.

(5) Galvanic angular deviation (positive pole to right) produced a deviation of 180° to the right and no vertigo.

(6) Galvanic angular deviation (positive pole to left) was through an angle of 180° to the left. There was no vertigo, and no inclination of the head was present after the tests.

These tests indicate a hypersensitive state of both vestibular systems.

Case 6.—J. W., aged 47, a slaughterman and tripe-dresser, was "feverish" for a week during February, 1924. On going to the station one evening he found that he was unable to walk straight, and felt top-heavy; he had to hold on to railings, &c., to prevent himself falling. Thinking that he needed a stimulant, he tried to go to a convenient public house, and felt that he was never going to reach it. After a small draught of spirits he commenced his journey home, and it took him half-an-hour to cover a distance of some 150 yards, owing to the severe vertigo which he experienced. He had no double vision. He slept well, but when he woke the next morning he saw double for the first time. When seen that day he had also strabismus and nystagmus. The pupils were normal and there was slight pyrexia. He was unable to stand up owing to vertigo, even with his eyes open, so it was concluded that Romberg's sign was positive. He had no headache or pain, but felt extremely weak, so much so that he felt unable to move in bed. There were no signs of paralysis and the patient was able to swallow and speak without difficulty. The reflexes were exaggerated. Delirium developed, and he can still recall its "occupational" nature, which agrees with the reports of his relatives. In his delirium he quarrelled with his employer, gave in his notice, then proceeded to the seaside and there signed a contract for three years with another firm. At other times he saw a church, to which came a constant succession of wedding parties. The significance of this was, at first, obscure, until it was ascertained that next door to the shop where he was employed there is a bakery which caters for wedding parties.

The delirious state lasted a fortnight, with accompanying diplopia and strabismus. Vertiginous attacks occurred in bed. There was no marked lethargy or insomnia, and after a rest in bed for six weeks he was allowed up, apparently completely recovered.

His present state of health is good. He shows no post-encephalitic phenomena, and apart from occasional neuritic pains in his chest and arms, he feels as well as ever and is able to perform his work with his usual zest and vigour. There is a slight deviation with extended arms. The results of the cold caloric tests were as follows: with the right ear, nystagmus occurred in 36 sec.; with the left ear it occurred in 45 sec.

A complete examination of every system revealed nothing else abnormal, but the results of the Babinski-Weill reactions are very interesting. They are as follows:—

(1) The gait is normal.

(2) Spontaneous angular deviation—90° to right.

(3) Caloric angular deviation (cold water in right ear)—225° to right with no vertigo.

(4) Caloric angular deviation (cold water in left ear)—270° to left with some vertigo and a reeling gait.

(5) Galvanic angular deviation (positive pole to right)—360° to right.

(6) Galvanic angular deviation (positive pole to left)—360° to left.

Although this patient does not complain of vertigo or show nystagmus, these results point to both vestibular tracts being in a hypersensitive state.

There can be no doubt that the last four cases are cases of epidemic encephalitis. Each has vestibular phenomena, but the times of occurrence of these phenomena have shown the widest possible divergence. They have occurred at the onset, during the acute phase of the illness, and for the first time as residua or they have persisted as such.

Case 3 had at the onset severe vertigo which has persisted and is associated with nystagmus, a tendency to Rombergism and hypersensitiveness of the right vestibular connections and hyposensitiveness of the left vestibular connections.

Case 4 had an onset with nystagmus, tinnitus and vertigo on closing the eyes (? Rombergism). Vertigo and nystagmus have persisted, and both vestibular systems are in a hypersensitive state.

Case 5 had nystagmus and deafness at the onset, and after an almost complete recovery developed vertigo and nystagmus a year later. He is now becoming more and more Parkinsonian and suffers from severe vertiginous attacks from time to time.

Case 6 had an extremely severe vestibular onset with vertigo and Rombergism, before diplopia appeared. To outward appearance recovery has been complete, but here again there is a hypersensibility of both vestibular tracts.

All four cases show abnormal Babinski-Weill reactions and some deviation of the hands when the arms are outstretched and the eyes shut. (Hautant's test.)

The following cases were selected from the clinic of Dr. A. J. Hall, of Sheffield. The criteria for selection were spontaneous nystagmus and external ophthalmoplegia. I am indebted to Dr. Hall not only for his kindness in allowing me to see these patients, but also for notes on the history of the cases, which are described below.

Case S 1 E. D., female, aged 41, was first seen in April, 1924, when she had lalling speech and right facial paralysis. She complained of headache and was emotional. There was a history of "influenza" two or three weeks earlier, which began with headache, sore throat and slight dysarthria. The speech grew worse and she was unable to put out her tongue. She had diplopia and slight pyrexia. Her husband had "influenza" about the same period. On examination she showed slight nystagmus and right-sided facial paresis. The tongue was put out with difficulty, and it showed marked deviation to the right and hollowing. There was no dysphagia, insomnia or lethargy, but dysarthria was present. When admitted to hospital a month or so after onset, she showed "lalling" speech and slight ptosis. The pupils were normal; diplopia was absent. The abdominal reflexes were more marked on the right side than on the left. A week later the patient vomited and at this period the pupils were unequal, the right side being the larger. The right-sided facial palsy still persisted and there was weakness of the right hand. Palilalia was still present and the patient became very restless and complained that she became tired when masticating her food. After an improvement in her speech and general condition, she lost her speech for about a quarter of an hour whilst attending service in November, 1924. The following day she was again speechless for an hour and was unconscious for another hour. She also complained of aching of the legs. Months later she complained of pains and strange sensations down the right and left sides of the body. The sensations began as a numb feeling in the cheek, passing down to the arm and knee as "pins and needles." The arm was jerked backwards and forwards and an attack lasted about five minutes or more.

The Babinski-Weill reactions were carried out by me with the following results:

Spontaneous angular deviation: 45° to left,

Caloric angular deviation, cold water to right ear: 180° to left. There was obviously a strong tendency to fall to the right side and the patient admitted this and that she did her best to correct it. Vertigo was severe.

Caloric angular deviation, cold water to left ear: 45° to left. Patient was very dizzy. The test was stopped after three trips on account of the severe vertigo.

Galvanic angular deviation, positive pole to right: 45° to right. Slight vertigo.

Galvanic angular deviation, positive pole to left: 90° to right. Vertigo. There was a definite tendency to fall to the left, but this was again corrected by the patient.

Even when simply blindfolded the patient showed that her equilibrium was unstable by the unsteady and uncertain gait. Owing to the severe reactions produced it was impossible to carry out all the tests completely, but the above results and the symptoms displayed indicate that both vestibular systems are much more sensitive than normal.

Case S 2.—W. W., aged 45. (This is the patient already referred to in the

text, as one in whom ptosis and ophthalmoplegia were temporarily and partially relieved by syringing the ears with cold water.) He left off work in March, 1924, having been drowsy for the two previous weeks. The following September he complained of insomnia, which was relieved by milk injections and has not appeared since. In April, 1925, he developed a drooping right lid and almost complete ophthalmoplegia. The pupils reacted to light and nystagmus was present. In November, 1925, he had marked ptosis on the right side, nystagmus and an ophthalmoplegia which was practically complete. He complained of diplopia.

The results of the Babinski-Weill reactions were as follows :—

Spontaneous angular deviation : 45° to left.

Caloric angular deviation (cold water to right ear) : 360° to right. The gait was very unsteady and vertigo occurred.

Caloric angular deviation (cold water to left ear) : 270° to left. The gait was again unsteady and vertigo was present. After this test the patient stated that his diplopia had disappeared.

Galvanic angular deviation (positive pole to right) : 270° to right.

Galvanic angular deviation (positive pole to left) : 90° to left.

These results indicate that both vestibular systems are hypersensitive ; this case also serves to show the importance of vestibular control over eye-movement.

Case S 3.—A. D., aged 39, male. This patient was admitted to hospital in June, 1921. He dates his present condition from an acute febrile illness which occurred two years previously. He was then in bed for four days only and was not particularly sleepy. On admission he complained of difficulty in walking and weakness and tremor of the arms. He had a well-marked "fixed expression." The pupils were unequal and nystagmus was present. No other cranial nerves were affected. These features are still present and there is a typical flexed posture of the hands with fine tremor at times. He is unable to open his hands quickly and fully. His gait is of a shuffling, festinating character, and once started he has difficulty in stopping himself. In the street he has to stop himself against some object when he wants to change direction. When stepping backwards he cannot stop and falls unless he comes up against something. He is powerfully built, but states that he is now much weaker than he was.

The Babinski-Weill reactions were as follows :—

Spontaneous angular deviation : 45° to right. The patient did not fall when walking backwards, but he had great difficulty in stopping.

Caloric angular deviation (cold water to right ear) : 180° to right, in three trips only. The patient then fell backwards. Vertigo and nausea were absent.

Caloric angular deviation (cold water to left ear) : There was only a slight deviation to the left in three trips. This test was abandoned because the patient was unable to stop himself when walking backwards.

Galvanic angular deviation (positive pole to right) : 90° to right in two trips before falling backwards.

Galvanic angular deviation (positive pole to left): 90° to left in two trips before falling backwards.

These results are gravely complicated by the patient's inability to carry out his part of the tests successfully. None of the tests were completed, but the resultant deviations, except in one case, are greater than the normal for the number of trips performed.

Case S 4.—G. C., aged 20, male, was drowsy for eight or nine weeks during the summer of 1922. He was difficult to wake for meals and his eyes were "funny." He "used to rave terribly," and he had somnambulism. Whilst in hospital he had trouble with his right atrium and his ear discharged. The following November he became drowsy again, with intervals of restlessness. He "gasped" in his sleep and made strange noises. He was slow over his meals and salivated profusely. The facies was not definitely Parkinsonian and he was quite quick in his movements. The gasping whilst asleep continued, and unless his feet were put down firmly they dithered. Months afterwards his face was fixed and there was a general facial weakness which was greater on the left side. The trunk was bent and the left arm was stiff. His speech was thick and there was salivation. In May, 1925, he started to complain of great thirst and passed large quantities of urine. He ate well, but lost weight. Examination of the urine showed neither albumin nor sugar and the specific gravity was 1002. He is still very thirsty and always carries a supply of water with him. The salivation has decreased with treatment by belladonna. Nystagmus is present.

The Babinski-Weill tests gave the following results:—

Spontaneous angular deviation: 30° to left.

Caloric angular deviation (cold water to right ear): 30° to right.

Caloric angular deviation (cold water to left ear): 180° to left. Vertigo.

Galvanic angular deviation (positive pole to right): 90° to right.

Galvanic angular deviation (positive pole to left): 90° to left.

In view of the history of ear trouble in this case nothing definite can be said about these results.

These four cases had established post-encephalitic residua. All have shown nystagmus at some period or other and three show Babinski-Weil reactions which must be considered abnormal. In view of the fact that I have no evidence as to the value of these reactions when ear trouble is present no attempt is made to interpret the results obtained in Case S 4.

Diagnosis.

The diagnosis of the abortive or aberrant types of a disease such as epidemic encephalitis is always difficult. It must never depend on the presence or absence of a certain symptom or syndrome, but must be arrived at only after a careful consideration of the onset and course of

the illness, and by an equally careful exclusion of all other pathological processes which might produce similar manifestations.

There is a grave danger in labelling obscure nervous cases with the name of this almost untreatable malady, and a diagnosis of vestibular encephalitis should not be made until all other conditions such as syphilis, otitis interna, &c., have been excluded. The history of an "influenza-like" illness is often too readily elicited, and to place such reliance upon it that more likely lesions are excluded, deprives the patient of the chance of cure, if the real condition be curable.

Where the illness has been accurately observed, or where there are other encephalitic residua present which we know can be caused in no other way, the diagnosis is rarely open to doubt. Of the more or less "pure" cases (Cases 1 and 2) described above, the second gives a history of what probably was an attack of encephalitis, and the first gives a history of vertigo followed by lethargy, occurring about the same time as another definite case with which she had been in close contact. The likelihood of infection in this case is very great. In connection with the possibility of direct infection, it should be stated that about the same period, in the same district, two cases were seen in one household.

Ménière's disease was the diagnosis which was made at first, but the absence of tinnitus and deafness and the presence of ptosis, together with the history, excluded this condition.

Great difficulty may arise in these vestibular cases in deciding whether an intracranial tumour is present or not. In cases of cerebral tumour, early and projectile vomiting, headache, and optic neuritis are present in about 80 per cent. of all cases, and localizing signs appear and gradually become progressive, as the tumour increases in size.

Tumours of the cerebello-pontine angle can only be excluded with difficulty. An important diagnostic difference, however, in this form of new growth is the presence of a nerve deafness with tinnitus, the deafness gradually becoming complete. Vertigo and nystagmus also occur. Interference with the function of the fifth and seventh cranial nerves may occur, but this by no means excludes epidemic encephalitis. Bárány's tests appear to give normal results in these "extracerebellar" tumours, so that some importance may be attached to these, but in doubtful cases with no definite history careful observation over a varying period of time will definitely clear the issue.

Tumours of the cerebellum may be suggested, but the presence of

ataxia, reeling gait, dysdiadochokinesia, atonia, &c., and the absence of Romberg's sign are suggestive. Nystagmus on looking towards the lesion and vertigo away from the side of the lesion are important signs. The condition is progressive and extension may cause pressure on the sixth nerve and on the pons, giving rise to a spastic hemiplegia on the opposite side. It should again be pointed out that cases of epidemic encephalitis have occurred showing signs of cerebellar involvement, whilst no lesions were found in the cerebellum at autopsy.

A "syndrome of the vestibular nuclei" is described by Tilney and Riley [48] as follows: Paroxysmal vertigo, with intervals of freedom or negligible symptoms; loss of equilibratory control; normal hearing; absence of any other somatic motor or sensory disturbance, or of any splanchnic motor or sensory symptoms. No pathological instance is given, but in vestibular encephalitis we have at least one example which justifies the separation of such a syndrome, which may or may not be accompanied by other symptoms due to involvement of adjacent nuclei.

The presence of nystagmus may suggest a diagnosis of disseminated sclerosis, especially in Parkinsonian cases where troubles of speech are present. Moreover, according to Charcot, vertigo occurs in three-quarters of cases of this disease, and there may be diplopia as an initial symptom. The disorder of speech in this condition is essentially a difficulty in enunciation, whilst in encephalitis the speech may be affected in various ways from aphasia to dysarthria. The spasticity of disseminated sclerosis shows exaggerated deep reflexes and Babinski's sign is rarely absent. In encephalitis, limbs that are rigid may show variable reflexes and Babinski's sign is rare. In insular sclerosis optic atrophy is common; it is rare, some think unknown, in epidemic encephalitis. Remissions are a typical feature of both diseases. The exclusion of disseminated sclerosis where there is nystagmus, disordered speech, tremor and a spastic paralysis is impossible, unless in the presence of a very reliable or typical history, or where some well-marked post-encephalitic residua are present.

Griffiths [25] has described an acute cerebellar encephalitis in children from 3 to 12 years of age. The onset is sudden and there is a staggering gait, with ataxia, disturbance of speech, nystagmus and strabismus. Vertigo was not as a rule reported in the literature reviewed by him, but he thinks that it may have had some influence in the production of the staggering gait. There is no evidence that the vestibular tests were performed, but in the light of the material which is set forth elsewhere it is possible that these were cases of vestibular encephalitis.

A similar condition—an acute serous encephalitis—was recently described by Brown and Symmers [9], who claim that this is a newly-recognized disease of childhood. The onset is sudden, with fever, ptosis, strabismus, nystagmus, hemiplegia and bulbar paralysis. Coma and convulsions occur and death ensues in thirty-six to forty-eight hours. Localizing signs may be present.

When the vertigo causes the patient to fall, epilepsy is naturally suggested, but in vestibular encephalitis there is no loss of consciousness; indeed, the patient is very acutely aware of what is happening to him, and the common diagnostic features of the epileptic fit such as the aura, the tonic and clonic stages, biting of the tongue and involuntary micturition are absent. Pierre-Marie and Pierre [38] have studied the vestibular function in epilepsy. They found that in *petit mal* it was difficult to determine any difference from the normal, whilst in epileptics who had major attacks there was great variability in the reactions, exaggeration alternating with depression. These observations are not of great help in excluding vestibular encephalitis where a similar variability exists, but they are certainly of great interest.

The triad described by Barré and Reys and consisting of nystagmus, Romberg's sign and abnormal Babinski-Weill reactions, is of importance in suspected "pure" cases of vestibular encephalitis. The value of Rombergism is open to doubt, so I venture to suggest another triad as follows: Disorders of equilibration, e.g., vertigo and including Rombergism; spontaneous nystagmus; abnormal induced nystagmus, or abnormal Babinski-Weill reactions.

A patient may have vertiginous sensations and show no Rombergism, or nystagmus may not be spontaneous, but may be easily induced, or the Babinski-Weill reaction may show abnormal deviation. If organic ear disease can be excluded, the presence of any two of these phenomena which constitute the triad can be adopted as clinical evidence of disordered vestibular function.

Prognosis.

In contrast with the amount of fact which has been established regarding the clinical manifestations of epidemic encephalitis, there is but a scanty array of data upon which a reliable prognosis can be made in any given case. It would appear that every encephalitic is a law unto himself. The progressive or recurrent course of chronic encephalitis makes the outlook one which is extremely difficult to estimate, and it would seem that almost anything can happen to an encephalitic,

except, perhaps, complete recovery. This vague but grave prognosis is not greatly altered in the vestibular variety.

Gerlier was of the opinion that the condition as seen by him was not very serious, except for its incapacitating effect. In my own brief series of cases there are no grounds for the making of dogmatic statements as regards the outlook, as the following brief review will show :—

Case 1 still has vertiginous attacks, &c., but has recently improved. Case 2 has shown little or no change for over a year. Case 3 is also apparently at a complete standstill, although luminal appears to have relieved the tremor and the disturbances of sleep. He is now very melancholy. Case 4 is going steadily from bad to worse. Case 5 made what appeared to be a complete recovery except for some ptosis, slight tremor and myoclonus, only to be attacked months later with vestibular symptoms. His general condition has improved with treatment by belladonna. Case 6, after a severe vestibular onset is now in good health, except for transitory neuritic pains in the thoracic region.

Prognosis in such cases, as in all other cases of epidemic encephalitis, should be very guarded. Each case should be studied apart from others, and any statements made concerning recovery should be qualified by an explanation of possible eventualities.

Treatment.

When the question of treatment arises we find ourselves practically impotent. The varied treatment of epidemic encephalitis need not be dealt with here, but an account of the attempts to alleviate the symptoms of the vestibular variety must be added.

The régime advocated by Gerlier can scarcely be improved upon, even with our modern resources. He advised rest, general hygiene. disinfection and "Sunday closing." He got no constant results with drugs. Nux vomica and valerian were unreliable, quinine was useless, but the iodide of potash was employed with some success. In the treatment of *kubisagari* Castellani and Chalmers [12] advise removal from the endemic area or from the close proximity of stables, and the use of a mixture containing arsenic and the iodide of potash. Quinine is an accepted remedy for vertiginous attacks. It is strongly recommended by Charcot in the treatment of Ménière's disease. According to Scott [42] minute doses are sedative to the labyrinthine system, whilst large doses act as an irritant. The results obtained with it in ordinary cases may be due to its anti-catarrhal action. Barré and Reys

speak of the happy effects they obtained with the drug, but in my series of cases the hydrobromide was tried with little or no result. These French observers also employed a cachet containing stovaine, pyramidon and veronal.

Bromides, with and without the iodide of potash, were also used by me in the hope of diminishing the reaction to vestibular disturbance, but it cannot be said that this hope was fulfilled.

Only one case (Case 3) in the series showed symptoms which suggested treatment with hyoscine, but the results obtained in this particular case, by giving 2 grains of luminal at bedtime, were so good that it was never tried. Whether or not a period of calm coincided with the commencement of luminal treatment it is difficult to say, but the tremor has certainly diminished and is, at present, often absent for days together. Vertiginous attacks still occur, but the sleep has become more normal and the patient has felt in a smaller measure the same tonic effect from the drug, which has raised epileptics from their former bromide stupor. Luminal was tried in the other cases with some success.

Of all the therapeutic measures employed the most effective was rest. Freedom from worry and fatigue was beneficial in all cases, and anxiety or exertion was, as a rule, surely followed by a relapse. A change of air and scene has also been beneficial in two cases. No attempt at dieting was made, nor does there appear to be any indication for supervision in this direction.

It may be concluded then, that apart from luminal, drugs are of little value in the treatment of vestibular encephalitis. Rest is an all-important and effective measure and should, if possible, be prolonged and accompanied by a change of climate and surroundings.

Conclusions.

It must be acknowledged, after the evidence brought forward, that the vestibular mechanism can be and is interfered with in epidemic encephalitis. The author's cases have not been selected; they are the only survivors of epidemic encephalitis who could be traced in a private practice, and they all live within an area of half a square mile. These facts have led the author to believe that such cases must be numerous, especially as six samples have occurred in such a limited area.

Moreover, a better explanation of the multiplicity of the eye symptoms in encephalitis cannot be offered than that they are produced,

(1) *Vestibular syndrome* :—

Vertigo.

Nystagmus.

Abnormal induced nystagmus or abnormal Babinski-Weill reactions.

(2) *Juxta-vestibular syndrome*, with signs pointing to involvement of structures, adjacent to or connected with the vestibular nucleus :—

Oculo-motor symptoms.

Neuralgia.

Facial paralysis.

Salivation.

Disorders of respiration.

Disorders of pulse.

Vomiting.

Dysphagia.

Hypoglossal paralysis.

Pain in the neck and shoulders, &c.

(3) *Pallidal syndrome* :—

Tremor and rigidity.

(4) *Striate syndrome*, with involvement of the putamen and caudate nucleus :—

Tremor and myoclonus.

Combinations of any of these groups may occur, and it will be found that the only common symptoms which are not accounted for in this grouping are pyrexia and lethargy. Pyrexia may be the usual response to infection or it may be due to interference with the heat-regulation centre, which appears to be situated in the corpus striatum. Until the mechanism of normal sleep is better understood, no practical explanation of the lethargy can be formulated.

The following conclusions can now be drawn :—

(1) There is, in epidemic encephalitis, a definite affection of the vestibular apparatus and its connections.

(2) This affection of the vestibular apparatus may give rise to errors in equilibration, spontaneous nystagmus, abnormal induced nystagmus, or abnormal Babinski-Weill reactions.

(3) This vestibular syndrome may occur alone, or with symptoms, such as strabismus, or ptosis, &c., pointing to involvement of adjacent or connected nuclei, or with symptoms which indicate involvement of putamen and globus pallidus, such as tremor, rigidity and myoclonus.

(4) The vestibular syndrome may be present at the onset, or during the acute stages of the illness, or it may persist as a residuum.

not in the nuclei which preside over ocular motion, but in some centre which has the power of controlling or acting in conjunction with these nuclei. Such a centre is to be found in the vestibular nucleus, which, as we know, is connected with the oculo-motor centres, and encephalitic lesions are commoner in the region around the vestibular nucleus than they are in the region of the nuclei which control ocular movements. Any interference with the vestibular nucleus or the vestibular arcs will, therefore, disorganize the perfect responses to stimuli which pass through these arcs, and abnormal responses will result in abnormal ocular phenomena. The work of continental authors serves to show that residual ocular palsies can be temporarily alleviated by simple syringing of the ears. This has been confirmed by me in one case. In other words, vestibular stimulation is transmitted as usual to the oculo-motor centres, but the stimulus has to be abnormal or excessive before a response occurs. If there was a lesion of the oculo-motor centres themselves it is unlikely that vestibular stimulation could provoke any movement, so that these findings agree with the suggestion that the ocular phenomena of epidemic encephalitis are due to interference with the vestibular nucleus, arcs or nerve.

The occurrence of an encephalitic lesion in the corpus striatum might also interfere with the function of the vestibular nucleus, as the latter is connected with the globus pallidus by means of a recognized tract. In this case, a possible result would be the "release" of the vestibular nucleus, the restraining influence of the globus pallidus being removed, thus rendering the vestibular system hypersensitive, or, as the function of the globus pallidus seems to be primarily motor, the normal motor response to stimuli from the vestibular system would be deficient or exaggerated, thereby bringing the unconscious acts of automatic stabilization into the realms of consciousness, and producing symptoms of uncertain equilibrium such as vertigo. A more usual result of encephalitic lesions of the globus pallidus is the production of Parkinsonism with rigidity and tremor.

These symptoms in encephalitis can therefore be due to involvement of either the globus pallidus or the vestibular nucleus, or both, in each case with or without involvement of adjacent or connected structures.

Such a division would cover most cases of encephalitis, and it would be strictly in accordance with the appeal and need for a classification built up upon an anatomical basis.

The following classification is therefore suggested :—

The results in each individual case have already been given. They will now be summarized according to the test employed for the purposes of comparison:—

TEST 1.—Walking Up and Down.

Control No. 1	Aged 40	Gait normal.	No deviation.
,, ,, 2	,, 24	,, ,,	,, ,,
,, ,, 3	,, 38	,, ,,	,, ,,
,, ,, 4	,, 16	,, ,,	,, ,,
,, ,, 5	,, 34	,, ,,	,, ,,
,, ,, 6	,, 16	,, ,,	,, ,,
,, ,, 7	,, 27	,, ,,	,, ,,
,, ,, 8	,, 21	,, ,,	,, ,,
,, ,, 9	,, 45	,, ,,	,, ,,
Case 1	.. ..	Gait normal.	,, ,,
,, 2	.. ..	,, unsteady.	,, ,,
,, 3	.. ..	,, reeling.	,, ,,
,, 4	.. ..	,, normal.	,, ,,
,, 5	.. ..	,, unsteady and festinant.	,, ,,
,, 6	.. ..	,, steady.	,, ,,
Case S 1	.. ..	,, uncertain.	,, ,,
,, S 2	.. ..	,, unsteady.	,, ,,
,, S 3	.. ..	,, festinant.	,, ,,
,, S 4	.. ..	,, normal but slow.	,, ,,

TEST 2.—Spontaneous Angular Deviation.

Control No. 1	45° to left	Gait normal.
,, ,, 2	45° to right	,, ,,
,, ,, 3	30° ,,	,, ,,
,, ,, 4	90° ,,	,, ,,
,, ,, 5	30° ,,	,, ,,
,, ,, 6	60° ,,	,, ,,
,, ,, 7	30° to left	,, ,,
,, ,, 8	90° to right	,, ,,
,, ,, 9	30° to left	,, ,,
Case 1	45° to right	Gait normal.
,, 2	60° ,,	,, reeling.
,, 3	90° to left	,, unsteady.
,, 4	45° ,,	,, ,,
,, 5	90° ,,	,, ,,
,, 6	90° ,,	,, normal.
Case S 1	45° to left	Gait unsteady. Vertigo.
,, S 2	45° ,,	,, ,,
,, S 3	45° to right	Difficulty in stopping when walking backwards.
,, S 4	30° to left	Gait steady.

TEST 3.—Caloric Angular Deviation.

(*Cold Water to Right Ear.*)

Control No. 1	45° to right	Gait normal.	Vertigo.
,, ,, 2	135° ,,	,, ,,	No vertigo.
,, ,, 3	45° ,,	,, ,,	,, ,,
,, ,, 4	90° ,,	,, ,,	,, ,,
,, ,, 5	90° ,,	,, ,,	Vertigo.
,, ,, 6	180° ,,	,, ,,	,,
,, ,, 7	45° to left	Gait unsteady. Vertigo. Lateropulsion to right, but there was a definite attempt to correct, with resultant deviation to left.	
,, ,, 8	135° to right	Gait normal.	Vertigo.
,, ,, 9	90° ,,	,, ,,	,,

(5) Its occurrence is probably much commoner than the literature on the subject would appear to show.

(6) Interference with vestibular function can account for many, if not all, of the ocular phenomena of the disease.

(7) The separation of a vestibular and a pallidal syndrome serves to make a useful basis upon which can be built an anatomical classification, which would include all cases of epidemic encephalitis.

(8) Disorders of vestibular function may be added to the growing list of residual phenomena which warrant a retrospective diagnosis of epidemic encephalitis, if no other cause can be found.

(9) The possibility of a previous, current or impending attack of epidemic encephalitis should always be considered seriously in the differential diagnosis of cases showing disordered equilibration.

(10) If the theory is accepted that the virus of encephalitis obtains entrance to the central nervous system via the nasal mucosa and olfactory nerves, there is also another possible path along which it may travel to the brain. Like the viruses of measles and scarlatina, it may pass from the nasopharynx along the Eustachian tube to the middle-ear, where it may or may not give rise to symptoms such as pain and tinnitus. From thence it can pass along the eighth nerve to the vestibular nucleus, for which it has been shown to have a definite affinity in rabbits.

(11) The prognosis of vestibular encephalitis is very uncertain. The lesion is probably progressive and a recurrence of symptoms, from time to time, seems inevitable.

(12) In the absence of specific treatment, prolonged rest, freedom from worry and anxiety and change of scene are the most useful therapeutic measures. Of the many drugs which might be employed, luminal has given the best results. In cases with residual ocular paralyses, systematic syringing of the ears might conceivably encourage the re-establishment of complete ocular movement.

APPENDIX.

Babinski-Weill Reactions.

These reactions have been described already in the text. Three groups of cases were tested. The first consisted of nine apparently normal persons who acted as controls; the second consisted of my own six cases, and the third group consisted of four cases selected from those under the care of Dr. Hall.

Case 1	90° to left	Lateropulsion to left. No vertigo.
,, 2	No deviation	Slight lateropulsion to right, then after six trips, slight deviation to right. No vertigo. Slight nausea. Nystagmus.
,, 3	180° to right	Severe vertigo and slight nausea. Tremor of head. Nystagmus.
,, 4	90° ,,	Immediately on commencing trips, then through 180° to left. Very severe vertigo.
,, 5	360° ,,	Gait unsteady. Severe vertigo.
,, 6	225° ,,	Gait steady. No vertigo.
Case S 1	180° to left	Strong tendency to fall to right, which was corrected by patient. Severe vertigo.
,, S 2	360° to right	Gait very unsteady. Vertigo.
,, S 3	180° ,,	In three trips only. Patient then fell backwards. No vertigo.
,, S 4	30° ,,	Gait slightly unsteady.

TEST 4.—Caloric Angular Deviation.

(*Cold Water to Left Ear.*)

Control No. 1	90° to left	Gait normal.	Vertigo.
,, ,, 2	135° ,,	,, ,,	,,
,, ,, 3	90° ,,	,, ,,	,, Lateropulsion.
,, ,, 4	180° ,,	,, ,,	,,
,, ,, 5	45° ,,	,, ,,	Inclined to over-correct. No vertigo.
,, ,, 6	180° ,,	,, ,,	Vertigo.
,, ,, 7	135° ,,	,, ,,	,,
,, ,, 8	135° ,,	,, ,,	No vertigo.
,, ,, 9	180° ,,	,, ,,	Vertigo.
Case 1	90° to left	Gait normal.	No vertigo.
,, 2	45° ,,	Early counter-deviation to right.	Vertigo and nystagmus.
,, 3	90° ,,	Gait steady.	No vertigo. Nystagmus.
,, 4	360° ,,	In five trips only.	Very severe vertigo. No nausea. Slight nystagmus.
,, 5	360° ,,	Gait normal.	Slight vertigo.
,, 6	270° ,,	,, reeling.	,, ,,
Case S 1	45° to left	In three trips only.	Severe vertigo.
,, S 2	270° ,,	Gait very unsteady.	Diplopia gone.
,, S 3	Slightly to left	In three trips, as patient was unable to stop himself when walking backwards.	
,, S 4	180° to left	Vertigo.	

TEST 5.—Galvanic Angular Deviation.

(*Positive Pole to Right Side.*)

Control No. 1	90° to right	Gait normal.	No vertigo.
,, ,, 2	90° ,,	,, ,,	,, ,,
,, ,, 3	45° ,,	,, ,,	,, ,,
,, ,, 4	45° ,,	,, ,,	,, ,,
,, ,, 5	45° ,,	,, ,,	,, ,,
,, ,, 6	90° ,,	,, ,,	,, ,,
,, ,, 7	90° ,,	,, ,,	,, ,,
,, ,, 8	90° ,,	,, ,,	,, ,,
,, ,, 9	45° ,,	,, ,,	,, ,,
Case 1	90° to right	Gait unsteady.	Severe vertigo.
,, 2	45° to left	,, ,,	Slight ,,
,, 3	135° to right	,, ,,	No vertigo.
,, 4	45° to left	,, ,,	,, ,,
,, 5	180° to right	,, ,,	,, ,,
,, 6	360° ,,	,, ,,	Vertigo.
Case S 1	45° to right	Gait uncertain.	Slight vertigo.
,, S 2	270° ,,	,, unsteady.	,, ,,
,, S 3	90° ,,	,, festinant.	In two trips only. Patient fell backwards.
,, S 4	90° ,,	,, steady.	No vertigo.

TEST 6.—Galvanic Angular Deviation.

(*Positive Pole to Left Side.*)

Control No. 1	90° to left.	Gait normal.	No vertigo.
,, ,, 2	90° ,,	,, ,,	,, ,,
,, ,, 3	45° ,,	,, ,,	,, ,,
,, ,, 4	45° ,,	,, ,,	,, ,,
,, ,, 5	45° ,,	,, ,,	,, ,,
,, ,, 6	90° ,,	,, ,,	,, ,,
,, ,, 7	90° ,,	,, ,,	,, ,,
,, ,, 8	90° ,,	,, ,,	,, ,,
,, ,, 9	90° ,,	,, ,,	,, ,,
Case 1	135° to left	Gait unsteady.	Vertigo
,, 2	No deviation	,, normal.	No vertigo.
,, 3	,,	,, ,,	,, ,,
,, 4	135° to left	,, ,,	,, ,,
,, 5	180° ,,	,, ,,	,, ,,
,, 6	180° ,,	,, ,,	,, ,,
Case S 1	90° to right	Gait uncertain.	Tendency to fall to the left. Vertigo.
,, S 2	90° to left	,, unsteady.	Slight vertigo.
,, S 3	90° ,,	,, festinant.	In two trips only. Patient fell backwards. Slight vertigo.
,, S 4	90° ,,	,, steady.	No vertigo.

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THE ANATOMO-PATHOLOGICAL BASIS OF THE PARKINSONIAN SYNDROME FOLLOWING EPIDEMIC ENCEPHALITIS.

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PART I.

AN ACCOUNT OF PUBLISHED CASES.

IN a paper written in 1923 [18] reference was made to those cases of post-encephalitic Parkinsonism, few in number, in which the pathological findings had been reported. An account of a single personal case was given. During the past three years the literature on this subject has slowly accumulated, but is, as yet, comparatively small. The histological findings in single cases are reported by Scholz [22], Strauss and Globus [25], Claude and Schaeffer [2], Verga and Ulohogian [29], Tarozzi [26], Omodei-Zorini [21], and a few others whose papers, chiefly in Italian, I have been unable to obtain. It is proposed to give a summary of those papers in which two or more cases are reported. Creutzfeldt [4] refers to two cases of Parkinsonism examined histologically by Runge. The illness in the first of the two lasted sixteen months. In places, especially in the region of the substantia nigra, acute inflammatory changes were present such as are met with in the acute phases of epidemic encephalitis. There was, furthermore, a marked diminution in the number of cells of the substantia nigra. In the second case, Parkinsonism had been present for three years before death took place. The inflammatory changes were less striking as compared with the first case. Only a few of the cells of the substantia nigra remained. There was a marked increase in the glial element with fibre overgrowth. In neither of the two cases was there any noteworthy change in the pallidum or striatum. McKinley and Gowan [19] in a

recent publication give details of the microscopical findings in two fatal cases of Parkinsonism. The first case was that of a male, aged 27, who died six months after the acute attack of encephalitis. Apart from scattered perivascular infiltration with lymphocytes in the globus pallidus and putamen, no abnormality in the region of the basal ganglia was found. There was a marked outfall of the cells of the substantia nigra. Many of the cells which remained showed degenerative changes. In this region there was pronounced perivascular infiltration and an increase in the number of glial cells. The second case was that of a male, aged 20, who died three and a half years after the initial attack. Macroscopically, depigmentation of the substantia nigra was noted. Microscopically, the basal ganglia, pons, medulla and cerebellum were normal, except for a mild perivascular infiltration and here and there a discrete gliosis. The substantia nigra, on the other hand, was profoundly altered, there being considerable cell loss. Many of the surviving cells were atrophied. Gliosis was marked in this region. McKinley and Gowan used a micrometric method of counting the cells of the globus pallidus and substantia nigra and therefore their findings are of considerable value. In one other case previously reported by McKinley and in the two cases referred to above, there was no reduction in the cellular content of the globus pallidus, whilst the cells of the substantia nigra showed a reduction in their numbers varying between 57 to 87 per cent. Jacob [14] has examined, pathologically, five cases of Parkinsonism. In two of the cases some degenerative changes were apparent in the globus pallidus. In the remaining three cases changes in this region were unimportant. The substantia nigra in all five cases showed a dropping out of cells and the morbid changes in this region were, in every case, more marked than those found elsewhere. Jacob concludes that epidemic encephalitis commonly spares the cerebral cortex and finds its chief location, as a rule, in the substantia nigra. Verga and Ulohogian [29], in a male aged 19, who had suffered from Parkinsonism for four years, found no changes of note in the globus pallidus. The cells of the substantia nigra were definitely reduced in number and their place was taken by glial cells. The locus cœruleus showed the same alterations, though in a less marked degree. Their second case concerned a male Parkinsonian aged 30, in whom the disease had been present for two years. Very few of the pigmented cells of the substantia nigra remained. In this region there was marked proliferation of the neuroglial fibres. The cells of the globus pallidus appeared normal. Claude and Cuel [3] in two fatal cases of Parkinsonism found

marked alteration in the substantia nigra. The basal ganglia in each case were normal except for a moderate perivascular infiltration with round cells, which, however, was less evident than in the mid-brain. Freeman [10] has reported the histological findings in two fatal cases. The first case was that of a male, aged 38, who had an attack of epidemic encephalitis in March, 1920. Eighteen months later he began to show signs of Parkinsonism which became marked. Death took place in November, 1924. The cortex appeared normal. The basal ganglia were unaltered. The cells of the globus pallidus were present in normal numbers and they showed no chromatolytic changes. A slight degree of perivascular lymphocytosis was present in this region. The thalamus was unaltered. The substantia nigra was profoundly affected, the pigmented cells having almost entirely disappeared. Perivascular lymphocytosis was more evident in the region of the substantia nigra than elsewhere. The second case concerned a male, aged 20, who developed Parkinsonism three years after the initial illness. Macroscopically the substantia nigra appeared thin and grey. Microscopically insignificant changes were present in the cortex, corpus striatum, hypo-thalamus, cerebellum, brain-stem and cord. There was a marked decrease in the number of cells composing the substantia nigra. Gliosis and new vessel formation were prominent features in this region. In both cases Freeman noted a narrowing of the ansa lenticularis.

Spatz [23] refers, in a recent paper, to fifteen cases of Parkinsonism in which he has had an opportunity of studying the histological changes. He does not, however, give details of the cases. He comments on the outfall and high-grade atrophy of the cells of the substantia nigra in all the cases. The basal ganglia, which in the acute stages share in the widespread inflammatory process, are affected little or not at all. He further adds that the protean nature of the symptoms in the acute phase of encephalitis is due to the widespread and varying histological changes, while the constancy of the clinical picture in Parkinsonism depends on the outfall of the cells of the substantia nigra, which according to his experience is a constant finding. Foix and Nicolesco [9], as a result of an examination of material from five cases of Parkinsonism, conclude that the lesions preponderate in the region of the substantia nigra and that these are extremely well marked. The changes elsewhere, as in the globus pallidus, are much less in evidence. They lay stress also on the almost constant persistence of perivascular inflammatory changes especially in the region of the substantia nigra. Donaggio [6], in a paper read at the Medical Congress held in Brussels

in 1924, refers to his findings in three cases of Parkinsonism following encephalitis. In each case he found alterations in the substantia nigra. The basal ganglia, red nucleus and cerebellum showed no noteworthy changes. He lays emphasis on certain changes which he had found in the prefrontal cortex, the most important of which seem to be alterations in the neurofibrils of the cortical cells. From his findings he concludes that Parkinsonism is due to a combined lesion of the frontal cortex and substantia nigra. The most recent and at the same time the most important work on the pathology of Parkinsonism has been carried out by Hohmann [13], working under Professor Marburg in the Neurological Institute of the University of Vienna. Hohmann carried out a careful histological examination in eleven cases. In every case the most marked changes were found in the region of the substantia nigra. These consisted of a disappearance of a large proportion of the pigmented cells, destruction of many of the nerve fibres and a slight increase in the number of glial cells. Changes of importance were also found in the putamen and caudate nucleus, namely an outfall of the small polygonal cells, an increase in the glial element and lipoidal degeneration of many of the cells. The cells of the globus pallidus were involved to a less extent, as were the cells of the cortex and dentate nucleus. Hohmann agrees with the general findings of others to the effect that the substantia nigra is most involved in Parkinsonism, but owing to the widespread nature of the changes which were present in his own series of cases he is unable to make a definite statement as to the localization of the lesion responsible for the condition.

A consideration of the above reports in cases of Parkinsonism and of the findings in single cases reported by a variety of observers mentioned at the commencement of this paper and in a previous communication [18] leads one to the conclusion that changes in the substantia nigra consisting of an outfall of cells accompanied by varying degrees of neuroglial proliferation are the most marked feature of the histological picture in this condition. Most observers have found little or no change in the basal ganglia (except Hohmann). I have only been able to trace one case of Parkinsonism mentioned in the literature, in which the substantia nigra was reported as normal.

This case described by Hassin and Bassoe concerned a boy, aged 13, who in February, 1920, fell and struck his head. Soon after he complained of headaches with nausea and a moderate pyrexia developed. He was ill for sixteen months and was said to have had "sleepy sickness." He could not talk, became stiff and later developed convulsions. In

September, 1922, he showed a marked arching forward of the body in walking and a coarse tremor was present in his arms. The speech was slow and drawling and towards the end of his life dysphagia became marked. There is no mention of the presence or absence of involuntary laughter or crying. Post-mortem the cortex appeared normal. The small cells of the corpus striatum and cells of the optic thalamus had undergone chromatolysis with neuroglial cell increase. The blood-vessels in these two situations showed perivascular infiltration. The cells of the globus pallidus were normal both in number and appearance. A few blood-vessels here showed infiltration with round cells. The cell structure of the substantia nigra was well developed and there was no glial cell proliferation in this region. The tegmentum of the pons showed slight changes.

The authors consider the case to be probably one of post-encephalitic Parkinsonism and they comment on the normal appearance of the substantia nigra. Granted that this be a case of Parkinsonism following encephalitis, there are certain features in the case which suggest that the Parkinsonism differed from the usual type. Occasionally in persons under the age of 20, a type of Parkinsonism is met with in which there is a marked flexion forward of the body, often coarse tremor, marked dysarthria and a tendency to involuntary laughter. Rigidity is usually more marked on one side, the leg on that side being flexed. The general appearance of such a patient bears a fairly close resemblance to that seen in progressive lenticular degeneration. It would seem highly probable that the situation of the lesion underlying this variety of Parkinsonism differs from that found in the usual form. The case reported by Hassin and Bassoe may belong to this group. It should be noted that both the globus pallidus and substantia nigra were reported as normal. There is no mention in their account of the condition of the subthalamic nuclei.

PART II.

A Review of Recent Anatomical and Experimental work on the Substantia Nigra.

Within the last few years a number of anatomists and experimental workers have turned their attention to a study of the substantia nigra, as a result of the striking predilection which the encephalitic virus has shown towards this part of the mid-brain. It may be of interest, therefore, to review shortly our present knowledge of the anatomy of this mass of grey matter. I have derived a great deal of help in this direction

from a study of the recent book by Foix and Nicolesco, dealing with the anatomy of the basal ganglia and subthalamic region [9].

If a transverse section of the mid-brain at the level of the emergence of the third nerve be examined under a low power, one is struck by the large number of pigmented cells which form the substantia nigra on either side. Such an important collection of cells, far exceeding in number any other group in the brain-stem, must fulfil some important function. The substantia nigra is situated immediately dorsal to the pes pedunculi containing the pyramidal fibres. In a vertical direction it extends from the subthalamic region to the junction between the mid-brain and pons. In a transverse section through the mid-brain the substantia nigra can be seen, with the naked eye, as a broad dark band lying between the red nucleus and the pyramidal fibres. The colour is due to the black pigment which the cells contain. This pigment does not make its appearance until after the first few years of life and is not abundant until after the age of 20. In animals these cells contain no pigment. The substantia nigra consists of two parts: (1) zona reticulata which is placed ventrally and contains relatively few nerve-cells but is rich in nerve processes; (2) zona compacta which lies more dorsal; this comprises the main body of the substantia nigra. The cells are large and closely grouped together in islets. These islets can be roughly divided into three groups, external, middle and internal. The cells of the inner group are small as compared with those of the other two groups. A typical cell of the substantia nigra is elongated, multipolar, and possesses numerous dendrites. The pigment is generally grouped into a mass which lies towards one of the poles of the cell. It is from this pole that the axone arises. In a section stained by the method of Nissl the chromatin substance appears plentiful and is distributed throughout the cell except in the area occupied by pigment. The substantia nigra contains an extremely dense network of fibres. Towards its inner part, and tranversing it, are seen the bulky fibres of the third nerve. With regard to the course of the fibres of the substantia nigra these can be divided into two groups according to the direction which they take. The first group contains fibres which can be traced outwards and upwards. At the level of the mesial fillet, they bend sharply inwards so as to cross the fibres of the fillet at right angles. These fibres, although they do not form a compact bundle, are comparatively easy to follow up to this point in Weigert-Pal sections; they constitute the so-called "peduncle of the substantia nigra." Their ultimate destination is uncertain, but some, at least, join the fibres of the

posterior commissure, so crossing to the opposite side. (Foix and Nicolesco.) The second group of fibres comprise those that run ventrally into the midst of the pyramidal fibres and then appear to turn downwards. These fibres arise from cells of all parts of the substantia nigra, but more especially from those of the inner group.

With regard to the development of the substantia nigra, opinions are divided. Some anatomists believe that it arises as part of the mesencephalon, whilst others describe its origin from the diencephalon, from which the globus pallidus also arises. Upholding this latter view are Mirto and Spatz. Mirto [20], in 1896, suggested a close relationship between the globus pallidus and substantia nigra. He believed that they both originated from the diencephalon, but in the course of development became separated from one another by the posterior limb of the internal capsule. Spatz [24], in 1922, supported Mirto's theory as to the close relationship between these two structures, basing his opinion on the equally intense non-reaction shown by both these parts of the brain. Kappers [15] believes that the globus pallidus and substantia nigra have a common origin, namely from the sulcus limitans.

A study of the comparative anatomy of the substantia nigra brings out several points of interest. According to Foix and Nicolesco, in the mouse and guinea-pig the ventral zone, corresponding to the zona reticulata in man, contains many more cells than does the dorsal zone. The cells of the ventral zone are imbedded deep in the midst of the pyramidal fibres, which form a relatively much smaller tract than in man. Corresponding to the peduncle of the substantia nigra in man, an efferent bundle of fibres runs dorsally, outside the mesial fillet, to reach the tegmentum. These fibres seem to run towards the posterior commissure, some crossing the mid-line with the fibres of the commissure. Others can be traced as far as the anterior quadrigeminal body and the grey substance surrounding the aqueduct of Sylvius. In higher animals, such as the dog, a condition of affairs exists intermediate between that found in the guinea-pig and that in man. The pyramidal tract in the dog is bulkier than that of the guinea-pig. The ventral zone of cells is smaller, while the dorsal zone is larger, the reverse of that seen in the guinea-pig. In the human fœtus the disposition of cells resembles somewhat that found in the dog, the zona reticulata being more in evidence than in adult man. Foix and Nicolesco conclude that in animals the efferent path going dorsalwards, corresponding to the peduncle of the substantia nigra in man, is the more

important, while in man the fibres going into the pes pedunculi and turning downwards are the more numerous.

A certain amount of experimental work in connection with the substantia nigra has recently been carried out. Dresel and Rothmann [7] removed the cortex and corpus striatum on one side in dogs; a few of these animals survived the operation for some months. The substantia nigra on the side of the operation showed marked cell outfall and glial proliferation. They also performed bilateral decerebration in other dogs and the substantia nigra was found markedly altered on either side. In dogs, in whom the cortex alone was interfered with, no such changes in the substantia nigra were evident. These workers conclude, therefore, that changes in the substantia nigra occur as a result of interference with the corpus striatum, and are absent when the cortex alone is destroyed. Ferraro [8] in a recent extensive experimental research on dogs and cats comes to the following conclusions: (1) Extirpation of the cortex alone effects a reduction in the total volume of the substantia nigra on the same side, but the cells for the most part are conserved; (2) destruction of the corpus striatum, on the other hand, is followed by far-reaching degeneration of the cells of the substantia nigra. Some cell groups, however, seem unaffected and he concludes, therefore, that efferent fibres from the substantia nigra exist and that they may connect the substantia nigra with centres lower in the brain-stem. The experimental evidence afforded by these workers would suggest that any connections that may exist between the cortex and substantia nigra are unimportant, whereas fibres connecting the corpus striatum and substantia nigra do exist and they serve to link up closely these two parts of the extrapyramidal system.

Foix and Nicolesco sum up the connections of the substantia nigra in the following way: The efferent fibres can be divided into two main groups. The first comprises those fibres that penetrate into the midst of the pyramidal fibres and then turn downwards; presumably they link up the substantia nigra with centres lower in the brain-stem. The second group contains those fibres that form the peduncle of the substantia nigra; some of these fibres mingle with those of the posterior commissure and probably serve as commissural fibres between each substantia nigra; they may also connect the substantia nigra with other nuclei on the opposite side of the mid-brain. Foix and Nicolesco also suggest that there are other fibres in the peduncle of the substantia nigra which do not cross in the posterior commissure, but instead take a descending course and probably come into relationship with grey

masses lower down in the brain-stem. There would, therefore, appear to be two descending tracts and one ascending, chiefly commissural. It is evident, however, that we are yet completely in the dark as to the exact termination of these efferent fibres. With regard to the afferent fibres, the work of the Vogts [30], Wilson [31], Dresel and Rothmann, Ferraro and others, clearly shows the existence of important descending fibres from the corpus striatum to the substantia nigra, in particular from the globus pallidus. As to whether the cortex sends fibres directly to the substantia nigra, as upheld by Dejerine [5] and others, is more problematical. If such a connection exists, from the experimental work reviewed above, it would seem to play an unimportant part.

PART III.

Personal Findings in Eight Cases of Parkinsonism.

Methods used.—The following parts of the brain were examined in every case. Frontal, parietal, rolandic and occipital cortex; basal ganglia, subthalamic region, mid-brain, pons, medulla and cerebellum. In seven of the cases the lower half of the basal ganglia, the subthalamic region, mid-brain and upper pons were cut in serial sections. In an attempt to discover tract degenerations, this part of the brain in five of the cases was treated by the method of Weigert-Pal. At an earlier stage, however, frozen sections were taken from the mid-brain and stained by the methods of Nissl and Bielschowsky, and also by the Victoria blue method for neuroglia. Subsequently frequent sections throughout the series were stained with hæmatoxylin and van Gieson and by the method of Mallory In the remaining three cases the basal ganglia on one side were examined by the method of Weigert-Pal and the other side by the method of Nissl, the subthalamic region, mid-brain and pons being dealt with in a similar manner to that employed in the other cases. Particular attention was paid to the corpus striatum and to certain masses of grey matter in the subthalamic region, whose functions are unknown or uncertain, such as the substantia innominata of Reichert, the corpus Luysii, &c. Several control brains, sectioned and stained by the above methods, were used for comparison. At this point it may be mentioned that the study of the Weigert-Pal sections has proved very difficult and up to the present time no definite concluclusions have been arrived at regarding any secondary fibre degeneration that may follow a lesion of the substantia nigra. This part of the

work is being persevered with, and it is hoped that some definite results will soon be attained.

In various papers dealing with this and allied subjects such terms as the following are often met with: "The motor cells of the globus pallidus appeared normal in numbers," or "There was a marked outfall of the cells of the globus pallidus." Such expressions are somewhat vague, and in order to gain a rough idea of the relative number of cells in the globus pallidus, in normal as well as in pathological conditions, since 1923 I have employed a simple method of counting the cells which is as follows. A horizontal section, cut at approximately 15 mm., passing through the basal ganglia at about its centre, shows the globus pallidus divided into two segments, an outer and an inner. These are separated from each other by the internal medullary lamina. Such a section, stained by the method of Nissl, is examined with a two-thirds objective and a No. 4 eye-piece. The cells in six fields are counted; three fields being chosen from the outer segment and three from the inner. The fields should be so spaced that approximately the whole area of the globus pallidus is covered. In a number of normal brains I have found that the average count, per field, lies between forty and fifty. This method has been adversely criticized by McKinley and Gowan [19] and certainly it cannot compare for accuracy with their micrometric method, which, however, is too elaborate for ordinary routine laboratory work.

Before describing the findings in the cases of Parkinsonism, it may be of some interest to consider the acute stages of encephalitis, especially as to whether the mid-brain shows changes of greater intensity than those present elsewhere. The following is a short account, from the point of view of localization, of a fatal case of acute encephalitis of the choreiform type in a male, aged 18, in which death took place on the sixth day.

Macroscopically, intense congestion of the vessels in the region of the basal ganglia and mid-brain, more especially in the latter, was noted. Microscopically, the cortex showed a generalized discrete perivascular lymphocytosis, but was otherwise normal, no thromboses or hæmorrhages being seen. The basal ganglia on the left side were normal except for moderate inflammatory changes around the vessels. On the right side these changes were very marked in two situations, firstly between the globus pallidus and putamen, and secondly in the thalamus. There was, however, comparatively little infiltration of the surrounding parenchyma. A few of the cells of the globus pallidus showed neurono-

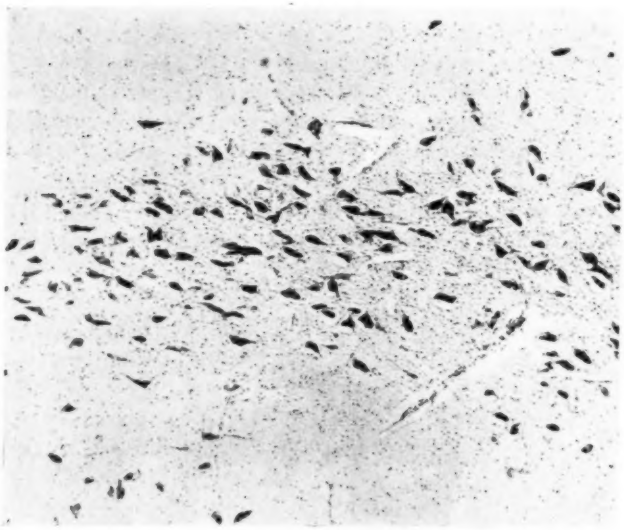

FIG. 1.—Normal substantia nigra. Zona compacta. Nissl's stain. × 120

FIG. 2.—Normal substantia nigra. Nissl's stain. × 70.

phagia but the majority were normal. In sections through the subthalamic region the perivascular changes were more marked, but they attained their maximum in the mid-brain. Here the vessels showed enormous cuffing, especially in the region of the substantia nigra and to a less extent in the grey matter underlying the aqueduct of Sylvius. In addition there was a general invasion of the parenchyma in these two situations with lymphocytes, &c., this again being definitely more intense in the substantia nigra. The relative escape of the red nucleus, considering its close proximity to the substantia nigra, was remarkable.

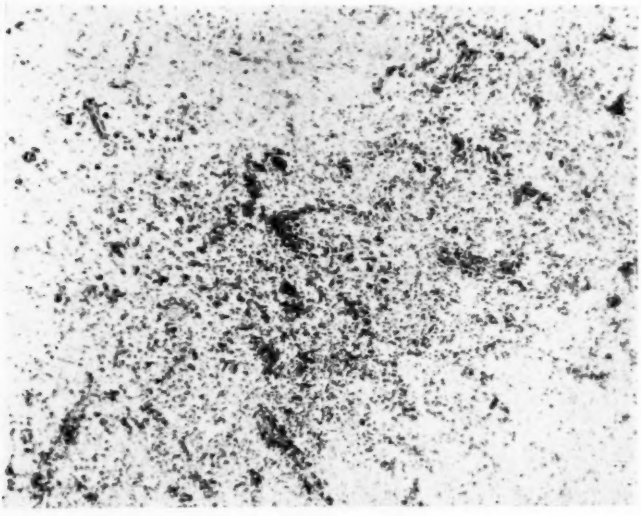

FIG. 3.—Substantia nigra in a case of acute encephalitis. Note the scattered pigment and lymphocytic infiltration. Compare with fig. 1. Nissl's stain. × 120.

The upper part of the pons showed similar, though less marked, changes especially in the region of the locus cœruleus. The lower pons, medulla, and cerebellum, beyond vessel infiltration, were normal. The inflammatory lesions in this case were widespread but certainly varied in intensity, being definitely more intense in the mid-brain, and especially in the substantia nigra, than elsewhere. The mid-brain from two other fatal cases of acute encephalitis occurring at a later age than the above case, showed intense inflammatory reaction in the mid-brain, both perivascular and parenchymatous. As in the above cases, these changes were most marked in the substantia nigra, many cells of which were

already depigmented or even destroyed. Similar cases have been reported in the literature. In a recent paper on "Encephalo-Myelitis following Vaccination," Turnbull and McIntosh[1] mention, *inter alia*, the distribution of the lesions in twenty-six fatal cases of the ordinary form of encephalitis lethargica. In eighteen of these, the mid-brain was most affected, and the substantia nigra almost invariably showed the greatest changes. From this evidence one may deduce the fact that the virus of epidemic encephalitis has a predilection for the mid-brain, and the substantia nigra in particular.

Pathological Findings in Eight Cases of Parkinsonism.

Case 1.—This case was fully described in a previous paper [18]. A short summary only will therefore be given.

Male, aged 41, had an attack of epidemic encephalitis in May, 1921. Diplopia, insomnia, and later lethargy, were present. He was acutely ill for four weeks. By the end of this period signs of Parkinsonism had shown themselves. When he first came under observation in September, 1922, this condition was present in a marked degree. At times he showed a slow rhythmical tremor in both hands. On September 26 he developed a pyrexia, and died on September 29.

Summary of histological findings.—The cortex was normal. There was no diminution in the number of cells in the globus pallidus and the majority appeared normal. "Calcification" of the vessels in the anterior half of the globus pallidus was marked. The putamen, caudate nucleus and thalamus were normal. The corpus Luysii was normal. The substantia nigra was profoundly altered on both sides, the outfall of cells being marked. Glial cell overgrowth was evident in the region of the substantia nigra. Perivascular lymphocytosis was more marked in this region than elsewhere in the brain. The red nucleus showed changes, especially with regard to the cells of the pars magno-cellularis. The cells of the locus cœruleus were not diminished in number; a few, however, were depigmented and showed chromatolytic changes. Other parts of the brain were unaltered.

Case 2.—Male, aged 43, had an attack of epidemic encephalitis in March, 1924, characterized by diplopia and insomnia followed by lethargy. He remained in hospital for four months. During that time he began to show signs of Parkinsonism. He was admitted to the Hospital for Epilepsy and Paralysis, Maida Vale, London, under the care of Dr. Wilfred Harris, in May, 1925. Akinesia and generalized hypertonus were so marked that he could not walk, and towards the end he was even unable to turn in bed without assistance. There was no tremor. He developed bed-sores and died on June 11, 1925.

[1] Turnbull, H. M., and McIntosh J. "Encephalo-Myelitis following Vaccination," *Brit. Journ. of Experimental Path.*, 1926, **7**, 181.

Histological Findings.

Cortex.—The cell structure of the various parts of the cortex appeared normal. Occasionally a vessel was observed which showed a discrete perivascular infiltration with round cells. The meninges were normal. There was no increase in the number of glial cells.

Basal ganglia.—The polygonal cells and Golgi 1 type of cell in both the putamen and caudate nucleus were normal in number and appearance. The cells of the globus pallidus were numerous. Using the counting method mentioned above, the average number of cells per field was forty-seven. For the most part the cells appeared normal. A very few were swollen and vacuolated.

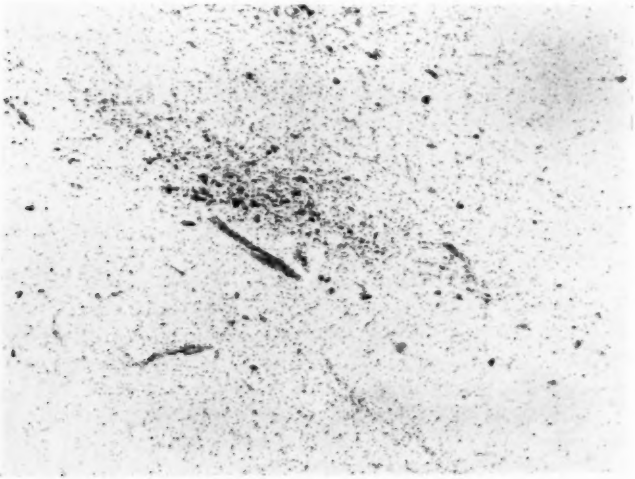

FIG. 4 (*Case* 1).—Parkinsonism; substantia nigra. Great reduction in the number of cells. Compare with fig. 2. Nissl's stain. × 70.

Many of the vessels presented an appearance of *état criblé*; some of them also showed a ring of lymphocytes. In the lower sections through the basal ganglia a considerable degree of perivascular lymphocytosis was present, especially near the ventricular edge of the thalamus. Two vessels in the anterior half of the globus pallidus contained a deposit of iron in their walls.

Thalamus.—No changes of importance were noted in the cell structure of the various nuclei.

Subthalamic region.—The cells of the corpus Luysii, substantia innominata of Reichert, and zona incerta were normal. In sections through the lower part of the subthalamic region, perivascular infiltration with round cells was noted, mesial to the corpus Luysii.

Mid-brain.—The cells of the third nerve nucleus seemed for the most part

unaltered. There was slight gliosis in the grey matter beneath the aqueduct of Sylvius. The cells of the red nucleus showed no changes of note. The substantia nigra was markedly altered on both sides. Very few pigmented cells remained. They were replaced by scattered masses of pigment and numerous glial cells. The zona compacta seemed to be slightly less affected in its outer half. The majority of the cells that were seen showed chromatolysis. The vessels in the region of the substantia nigra were encircled by several rings of lymphocytes; this inflammatory process was more marked in this region than elsewhere in the brain. The vessels of the corpora mammilaria were markedly engorged and some showed perivascular lymphocytosis.

Pons.—Slight inflammatory changes were apparent around some of the vessels in the grey matter underlying the aqueduct of Sylvius, where a moderate degree of gliosis was also noted. The nuclei of the middle cranial nerves appeared normal. The cells of the locus cœruleus on the left side were almost completely absent, scattered masses of pigment and glial cells having replaced them. The locus cœruleus on the other side was unaffected.

Medulla.—This appeared normal.

Cerebellum.—No noteworthy changes were present. A few vessels in the region of the dentate nucleus on either side showed a mild inflammatory reaction.

Summary of histological findings.—The cortex, lower pons, medulla and cerebellum were normal. The cells of the globus pallidus were not reduced in number and the majority were healthy. The putamen and caudate nucleus on either side were unaltered. Several periventricular vessels in the region of the thalamus showed considerable perivascular lymphocytosis. The various nuclei in the subthalamic region were normal. The substantia nigra on both sides was profoundly altered. A moderate gliosis was present beneath the aqueduct of Sylvius. The locus cœruleus on one side was practically destroyed.

Case 3.—Female, aged 38, had an attack of epidemic encephalitis in March, 1924, during the seventh month of a pregnancy. After her confinement she noticed a general weakness which gradually progressed. When seen in October, 1924, she presented a typical picture of severe Parkinsonism. There was no tremor. During May, 1925, she was admitted to Hanwell Mental Hospital on account of marked depression. Subsequently she attempted to commit suicide. On July 8 she had a syncopal attack, associated with a rise of temperature. During the next few days the pyrexia became more marked; death took place on July 16.

I am indebted to Dr. F. Golla for the opportunity of examining the brain, and also to Dr. F. Daniel for notes on the case whilst the patient was in Hanwell Mental Hospital.

Histological Findings.

Cortex.—The various parts of the cortex which were examined showed no changes of note, either in cell structure or in the appearance of the meninges or vessels. The subcortical white matter was normal.

Basal ganglia.—The putamen and caudate nucleus appeared normal at different levels. The cells of the globus pallidus were not appreciably reduced in numbers, forty-two cells being counted in each field. The cells in the outer segment were healthy, but in the anterior half of the inner segment some of the cells appeared shrunken and stained poorly. In this same region there was a considerable deposit of iron salts in the form of globules and in the vessel walls. One motor cell was observed which contained fine granules of iron. No neuroglial cell increase was apparent. Many of the vessels of the basal ganglia showed dilatation of their perivascular spaces, which in some

FIG. 5 (*Case* 2).—Parkinsonism ; substantia nigra. Compare with fig. 2. Nissl's stain. × 70.

instances contained a few lymphocytes. The cells of the thalamus, beyond containing a deposit of lipochrome pigment, were normal.

Subthalamic region.—The substantia innominata, corpus Luysii, and zona incerta showed no alterations of note.

Mid-brain.—A few of the cells of the third nerve nucleus on either side showed chromatolysis but the majority stained normally. The satellitosis, which is a normal feature of the cell structure of the red nucleus, was slightly excessive, but the cells themselves, for the greater part, were normal. The cells of the substantia nigra were greatly reduced in number. The majority of those that had survived showed chromatolysis. These changes affected both substantia nigra about equally and no part of the zona compacta was spared. In Bielschowsky preparations, the neurofibrils appeared considerably reduced

in numbers and the degenerative changes in the cells were well seen. In sections stained for neuroglial fibres both an increase in glial cells and fibres was apparent. The neuroglial cell most commonly met with contained a large pale staining oval nucleus and scanty processes. Astrocytes were abundant.

Pons, medulla and cerebellum.—No changes of note were present.

Summary of histological findings.—No abnormality in the basal ganglia was present except in the anterior half of the globus pallidus where an abundant deposit of iron was observed. In this region some of the cells appeared

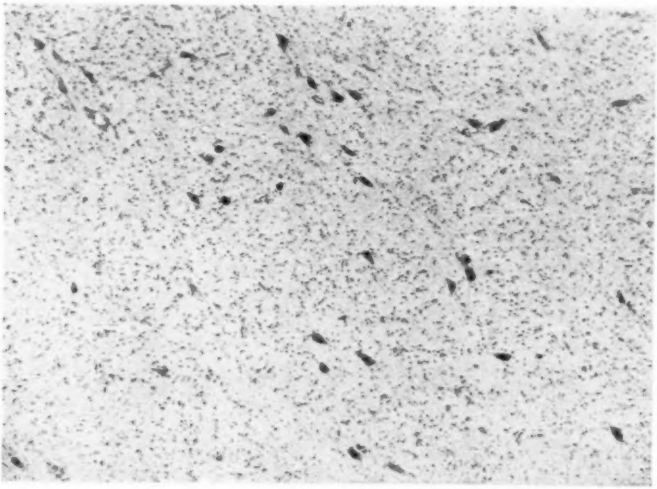

FIG. 6 (*Case* 2).—Globus pallidus. The cells appear normal. Nissl's stain. × 70.

shrunken. The vessels throughout the basal ganglia showed an *état précriblé* or *criblé*. The substantia nigra on either side showed a marked outfall of cells and neurofibrils. Glial cells and fibres were present in excess. No other changes of note were found in the rest of the brain.

Case 4.—Male, aged 20, had an attack of epidemic encephalitis in March, 1924. This illness was followed by nervous debility, but definite signs of Parkinsonism did not appear until July of that year. He was admitted to the Sheffield Royal Hospital under the care of Professor A. J. Hall in October 1924. He then showed extreme rigidity and bradykinesia of the Parkinsonian type with fixed immobile face, open mouth and marked sialorrhœa. Tremor was slight. He developed bed-sores and died on October 28, 1924, the temperature having steadily risen for some days before death took place.

Histological findings.

Cortex.—Various parts were examined; no changes of importance were observed.

Basal ganglia.—The putamen and caudate nucleus were normal; both the small and large types of cell were plentiful and stained well. The cells of the globus pallidus were normal for the most part: a few, however, appeared pale and shrunken. An average count of forty-two cells per field was estimated; it is possible that the actual number of cells was slightly below the normal. There were no deposits of iron in the globus pallidus nor increase in the glial element. The vessels of the basal ganglia were normal except for a moderate dilatation of their perivascular spaces; occasionally a discrete lymphocytosis around them was noted, especially in the thalamus, the cells of which were normal.

Subthalamic region.—On the left side the corpus Luysii, red nucleus, and substantia innominata were normal. On the right side a considerable degree of lymphocytosis around the vessels was apparent but the cells composing the various nuclei seemed to have escaped.

Mid-brain.—The nucleus of both third nerves appeared normal. The cells of the substantia nigra, especially on the right side, were much reduced in number. Chromatolytic changes, consisting of vacuolization, swelling of the cell body and eccentricity of the nucleus, were present in at least half of the cells that remained. Neuroglial cell increase was relatively slight, especially on the left side. The vessels on the right side of the mid-brain showed a considerable degree of cuffing; on the left side this was less evident.

Pons.—Discrete perivascular lymphocytosis of the vessels underlying the aqueduct of Sylvius was the only change of note, apart from a destruction of many of the cells of the locus cœruleus on one side.

Medulla and cerebellum.—Normal.

Summary of histological findings.—The cortex was normal. The cells of the globus pallidus were not appreciably reduced in number and the majority appeared normal, as did the cells of the caudate nucleus and putamen. Inflammatory changes in the basal ganglia were insignificant but were moderately severe around the vessels in the right subthalamic region. The substantia nigra showed definite changes especially on the right side. The vessels in the mid-brain, especially on the right side, showed marked cuffing. The locus cœruleus on one side was much altered.

Case 5.—Female, aged 27, had an illness in March, 1924, which lasted seven weeks and of which the details are unobtainable. By the end of April, 1924, symptoms and signs of Parkinsonism were apparent. She was admitted into the Sheffield Royal Hospital under the care of Professor A. J. Hall on May 26, 1924. She had a fixed expression, an open mouth, a general flexion forward of the head and trunk, with a typical posture of the upper limbs. There was some tremor of the lips but none in the limbs. Her condition gradually became aggravated. The temperature rose steadily for some days before death which took place on June 24.

FIG. 7 (*Case* 4).—Parkinsonism; substantia nigra. Compare with fig. 2. Nissl's stain. × 70.

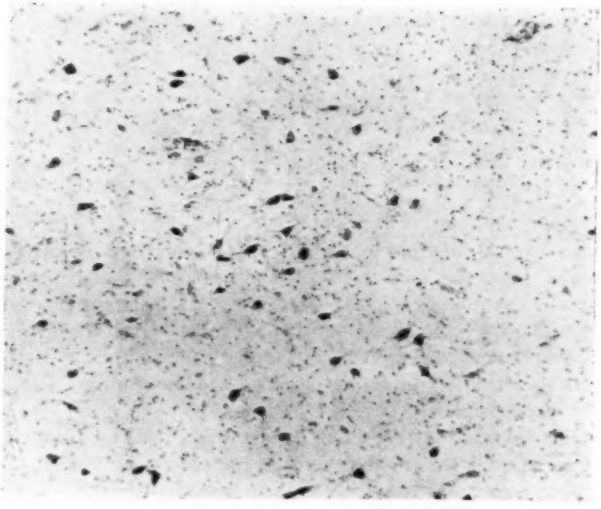

FIG. 8 (*Case* 4).—Globus pallidus. The cells appear normal. Nissl's stain. × 70.

Histological Findings.

Cortex.—This showed no abnormality.

Basal ganglia.—The cells of the putamen and caudate nucleus were normal. The cells of the globus pallidus were not counted; they appeared however to be numerous and, for the most part, unaltered. A moderate degree of perivascular infiltration was observed especially around vessels situated between the internal capsule and globus pallidus and to a less extent in the thalamus. No deposits of iron were observed. The neuroglial cells did not appear to be increased in number.

Subthalamic region.—On the left side the substantia innominata appeared normal. A considerable degree of gliosis was observed in two situations: (1)

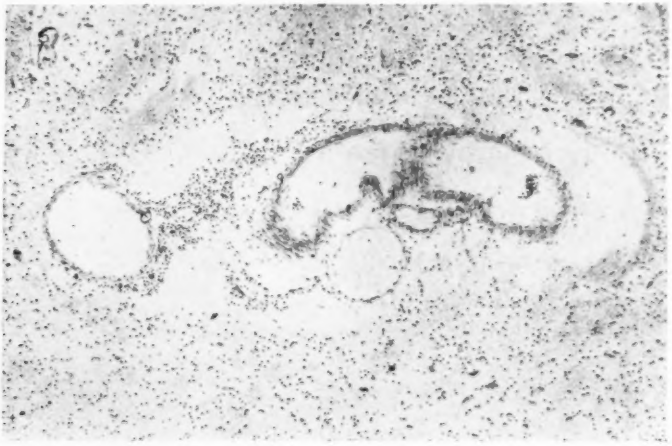

FIG. 9.—Parkinsonism. Typical appearance of a vessel in the basal ganglia, showing dilatation of the perivascular space and discrete lymphocytosis. Hæmatoxylin and eosin. × 70.

to the outer side of the red nucleus in the region of the mesial fillet, (2) between the red nucleus and the corpus Luysii. In the higher sections, in which these changes were apparent, no cells of the substantia nigra were seen, the sections being above the level of this nucleus. The affected area corresponded to that occupied by the substantia nigra. The corpus Luysii showed no apparent reduction in its cells, although there was a moderate increase in the number of glial cells.

Mid-brain.—The substantia nigra was profoundly altered on both sides. The cells were markedly reduced in number and the majority showed chromatolytic changes. Here and there, a small group of two or three cells, which appeared healthy, was noted. On the left side one such islet, situated in the lateral part of the zona compacta, containing about ten cells, appeared to have

escaped altogether. In Bielschowsky preparations the general picture shown by the Nissl sections was confirmed. The neurofibrils were scanty. In sections stained for neuroglia a great increase in the number of glial cells was apparent, many of them being rich in processes. Rod cells were plentiful especially in places where a few of the pigmented cells had escaped. In areas entirely denuded of cells astrocytes predominated. Apart from a discrete gliosis underlying the aqueduct of Sylvius the remainder of the mid-brain, including the third nerve nuclei and the red nuclei, showed no noteworthy changes.

Pons.—In sections through the upper part of the pons, slight gliosis was apparent in its dorsal portion. The cells of the locus cœruleus on the left side had practically disappeared. Only four or five cells remained as compared with forty to fifty on the opposite side. The site of the nucleus was merely represented by a scattered mass of pigment. In chromated sections stained by the method of Mallory many astrocytes were seen in this region. The locus cœruleus of the other side was normal. The vessels in the region of the iter of Sylvius showed a moderate degree of cuffing. In one particular section a vessel surrounded by a large cuff of lymphocytes was observed. In sections through the middle of the pons, the locus cœruleus on the left side showed similar changes to those just described, whilst on the other side a slight reduction in the number of cells was apparent. The vessel and glial changes were less evident at this level than in sections higher up, and in sections through the lower pons and medulla they were practically absent.

Cerebellum.—Beyond slight perivascular infiltration in the region of the dentate nucleus, the cerebellum appeared normal.

Summary of histological findings.—The cortex, putamen and caudate nucleus were normal. The cells of the globus pallidus were not counted but appeared plentiful and the majority were healthy. There was considerable gliosis in the subthalmic region without any definite evidence of changes in the neighbouring nuclei. The substantia nigra was profoundly altered on both sides. The red nucleus appeared normal. There was a moderate degree of gliosis in the periaqueductal grey matter. The majority of the cells of the locus cœruleus on the left side were missing and gliosis was apparent in the region of this nucleus. The remainder of the brain showed no noteworthy changes.

Case 6.—Male, aged 39, had diplopia in April, 1924, followed by fever, delirium, headache and lethargy. He was confined to bed for six weeks and thereafter made a slow recovery. Definite signs of Parkinsonism were noted in April, 1925. The akinesia and rigidity progressed rapidly, so that by the summer of 1925 he was bedridden. He was admitted to the Royal Sheffield Hospital in September, 1925. The rigidity was so marked that he could scarcely turn in bed. He developed a bed-sore and died on October 10, 1925.

Histological Findings.

Cortex.—Sections from the various regions of the cortex showed no abnormality of the meninges or cell layers. Very rarely a vessel surrounded by one or two rings of lymphocytes was seen.

Basal ganglia.—Horizontal sections through the upper part of the basal ganglia appeared normal, except for an occasional discrete perivascular lymphocytosis. In sections passing through the middle of the globus pallidus, the cells of the caudate nucleus and putamen appeared normal. No increase in the number of glial cells in these two nuclei was apparent. The cells of the globus pallidus, in Nissl preparations, appeared absolutely normal both in cellular structure and in numbers. An average count of forty-four cells per field was made. Some of the vessels here, as elsewhere in the basal ganglia, showed a dilatation of their perivascular spaces; exceptionally, a discrete lymphocytosis was found. There were no deposits of iron in the vessels of the globus pallidus. The various nuclei composing the thalamus on each side appeared normal, apart from deposits of a lipochrome pigment in their interior. This, however, was a common finding in controls. The ventricular edge of the thalamus showed a mild ependymitis. Perivascular lymphocytosis was more marked in the thalamus especially in the lower sections, than elsewhere in the basal ganglia. There was, however, little or no neuroglial cell overgrowth.

Subthalamic region.—Many of the cells composing the substantia innominata showed an eccentric nucleus, but a similar appearance was noted in several controls. The corpus Luysii contained well stained cells which appeared numerous. The upper part of the red nucleus beyond showing a satellitosis of many of its cells, which was also noted in controls, appeared normal. On both sides a marked increase in the number of glial cells was found in the grey matter underlying the aqueduct of Sylvius. Gliosis was also apparent on the left side in the region of the zona incerta. Many of the vessels in the subthalamic region, especially those occupying the anterior perforated spot, were surrounded by two or three rings of lymphocytes.

Mid-brain.—The gliosis underlying the aqueduct of Sylvius was marked and extended laterally. The cells of the third nerve nucleus seemed to have mostly escaped, but those occupying a dorsal and central position (i.e., those subserving the pupillary reactions) showed definite degenerative changes. The cells of the substantia nigra were reduced in number in a remarkable degree. A few of those that remained, scattered here and there in groups of two or three, appeared normal but the majority showed definite chromatolytic changes, such as swelling of the cell body, lateralization of the nucleus, extrusion of pigment, &c. Bielschowsky preparations confirmed the cell atrophy and other changes. Many of the neurofibrils had disappeared. Abundant new capillaries were observed in the region of the substantia nigra. Glial cells were abundant in this region. In neuroglial fibre preparations, a thick network of fine fibres was seen. The vessels in the mid-brain showed considerable perivascular lymphocytosis, especially those situated in the region of the substantia nigra. The red nucleus was normal. Sections through the lower part of the mid-brain and upper pons confirmed the gliosis in the periaqueductal grey matter, extending laterally to involve the locus cœruleus. The cells of this nucleus were probably reduced slightly in number. The majority showed degenerative changes, and scattered pigment was moderately abundant. The vessels in this

region appeared congested and a few showed a lymphocytosis. The nuclei of the various cranial nerves situated in the pons and medulla seemed normal.

Cerebellum.—The dentate nucleus on either side appeared normal, except for a discrete lymphocytosis around some of the vessels.

Summary of histological findings.—The cortex appeared normal. The putamen and caudate nuclei on either side were normal. The cells of the globus pallidus were normal in numbers and appearance, as were those of the thalamus. A moderate degree of gliosis was noted in the grey matter beneath the iter of Sylvius, both in the mid-brain and pons. The subthalamic nuclei were unaltered. The cells of the third nerve nuclei, which subserve the pupillary reactions, were degenerated. The cells of the substantia nigra on either side showed a remarkable reduction in their numbers. Gliosis and new

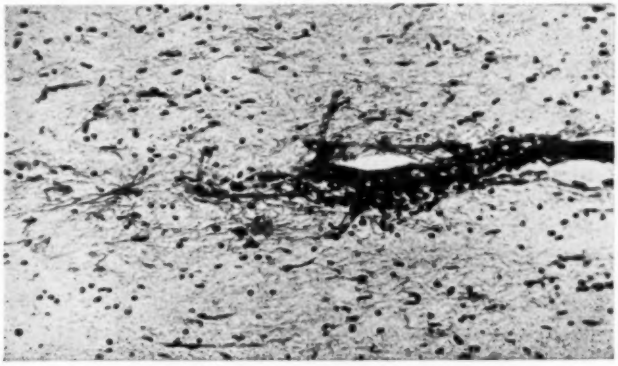

FIG. 10.—Parkinsonism. Gliosis around a vessel in the region of the substantia nigra. Victoria blue method (Anderson's modification). × 120.

capillary formation were evident in the region of the substantia nigra. The vessels in the mid-brain, especially those in the region of the substantia nigra, showed well marked cuffing. The locus cœruleus on either side was slightly altered. Other parts of the brain were normal.

Case 7.—Male, aged 23, was taken ill in April, 1924, with a general feeling of weakness which persisted for two weeks. Diplopia then appeared. He was admitted to hospital, where he showed some mental excitement, restless movements of the lower limbs and a moderate pyrexia. He refused to stay in hospital and returned home. He recovered slowly. Within the next few months his speech and movements became slow. He died suddenly of pneumonia on September 20, 1924.

Histological Findings.

Cortex.—This appeared normal everywhere apart from an occasional mild perivascular lymphocytosis.

Basal ganglia.—The putamen and caudate nucleus on either side showed no vessel infiltration nor neuroglial cell increase. The small polygonal cells were normal for the most part. The large motor cells in the putamen were more rounded than usual; some had an indefinite outline and an eccentric nucleus. The chromatin substance assumed the form of dustlike particles distributed towards the periphery of the cell. Satellitosis was normal in degree. Some of these findings were noted in controls. In addition, the material was poorly fixed. The cells of the globus pallidus stained feebly with Nissl's method. A cell-count showed an average of forty cells per field; it is possible that there was an actual reduction in the number of cells—though this must have been small. A mild degree of neuroglial cell overgrowth was apparent in the globus pallidus. Beyond an *tat précriblé* the vessels were normal and showed no deposits of iron. The cell structure of the thalamus was unaltered, although many cells stained poorly; this was attributed to the faulty fixation. No gliosis was noted. A few of the vessels in the thalamus showed a moderate perivascular lymphocytosis.

Subthalamic region.—The cells of the corpus Luysii appeared normal. The upper part of the red nucleus was unaltered, as were the cells of the substantia innominata.

Mid-brain.—On both sides the substantia nigra showed well-marked changes consisting of: (1) An outfall of cells; this was profound, especially in the mesial half of the zona compacta. In the lateral portion, here and there, small cell islets had escaped complete destruction; the majority of the cells showed chromatolysis. (2) Scattered pigment lying free in the parenchyma and in the perivascular spaces. (3) A marked increase in the number of glial cells, especially in the inner half of the substantia nigra. The majority of these cells possessed a large clear nucleus, containing scattered dots of chromatin. Red cells were fairly abundant. (4) A considerable degree of perivascular cuffing, to the extent of four or five rows of lymphocytes, was noted, and was more marked in this region than elsewhere. The capillaries were considerably increased in number. The red nucleus appeared normal. The cells of the third nerve nuclei were mostly unaltered, but some were definitely degenerated. A moderate degree of gliosis and vessel infiltration was apparent in the grey matter underlying the aqueduct of Sylvius, spreading laterally. In sections through the lower mid-brain and upper pons, the cells of the locus cœruleus did not appear appreciably diminished in numbers; several of them, however, showed lateralization of the nucleus with extrusion of pigment. Slight gliosis was noted in the region of this nucleus on either side. The lower pons, medulla and cerebellum were unaltered.

Summary of histological findings.—The cortex was normal. Many of the Golgi i. type of cell in the putamen and caudate nucleus showed changes, which were probably dependent on faulty fixation of the material. The cells of the globus pallidus were possibly slightly reduced in numbers. The thalamus and subthalamic nuclei appeared normal. The substantia nigra showed well-marked bilateral changes in its cellular structure, glial content, and in its

FIG. 11.—Control case. Normal appearance of fibres in the substantia nigra. Weigert-Pal preparation. × 70.

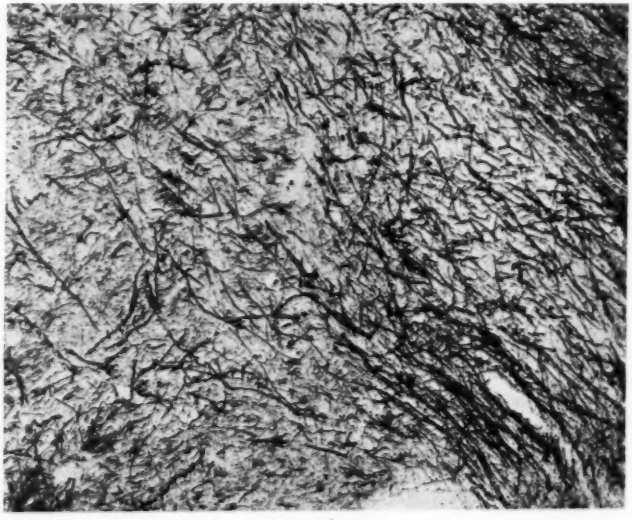

FIG. 12 (*Case* 8).—Parkinsonism; substantia nigra. Many of the fibres show beading and fusiform swelling of the myelin sheath. Compare with fig. 11. Weigert-Pal preparation. × 70.

vessels. A moderate degree of periaqueductal gliosis was noted. The locus cœruleus on either side showed minimal changes. Other parts of the brain were unaltered.

Case 8.—Female, aged 25, had an attack of epidemic encephalitis in March, 1924, during the seventh month of a pregnancy. Headache, diplopia, myoclonic movements, and lethargy were the chief manifestations of the disease. Within a few months Parkinsonism developed, and in November, 1925, this had attained considerable severity. She was attacked by facial erysipelas and died on November 24, 1925.

Histological Findings.

Cortex.—The meninges and cell structure showed no noteworthy changes. In the subcortical white matter a few vessels presented mild perivascular lymphocytosis.

Basal ganglia.—At all levels the putamen and caudate nucleus, on either side, appeared normal, and were devoid of gliosis or vessel changes. The cells of the globus pallidus, in Nissl preparations, appeared plentiful and stained well. A cell count showed an average of forty-one cells per field. The number of glial cells was possibly slightly in excess. The vessels of the globus pallidus, on either side, showed no changes beyond dilatation of their perivascular space. Many cells of the thalamus showed satellitosis and a deposit of lipochrome pigment; in other respects they were normal. In the more caudal sections through the thalamus the neuroglial cells appeared slightly increased in number.

Subthalamic region.—The corpus Luysii, upper part of the red nucleus and substantia innominata showed no noteworthy changes.

Mid-brain.—The pigmented cells of the substantia nigra on either side were markedly reduced in number. A few small scattered groups of cells remained, but of these few were healthy. The cell changes were uniform throughout the substantia nigra, affecting the mesial and lateral halves of the zona compacta about equally. Gliosis in the region of the substantia nigra was marked.

Summary of histological findings.—No changes of note were found except in the mid-brain.

PART IV.

Conclusions.

The cortex appeared normal in every case apart from occasional discrete perivascular lymphocytosis. Certain alterations in the appearance of the frontal cortex, stressed by Donaggio, have already been referred to. Hohmann also found cellular changes in the cortex. In view of the negative findings in this region by other workers, and the normal appearance of the cortex in the present series of cases, such

changes, when present, seem to be of minor importance. The caudate nucleus and putamen were normal as regards their cell structure in seven out of the eight cases. In one case (No. 7) many of the large cells appeared degenerated ; this may have been, in part, due to the fact that this particular brain was improperly fixed. Slight perivascular lymphocytosis was not uncommon and the vessels, in this region as elsewhere, showed almost constantly a dilatation of their perivascular spaces. Apart from Hohmann, other observers have described no noteworthy lesion in the putamen and caudate nucleus. Some of the changes, such as satellitosis and pigmentary degeneration, described by Hohmann in connection with these cells, were present in my controls

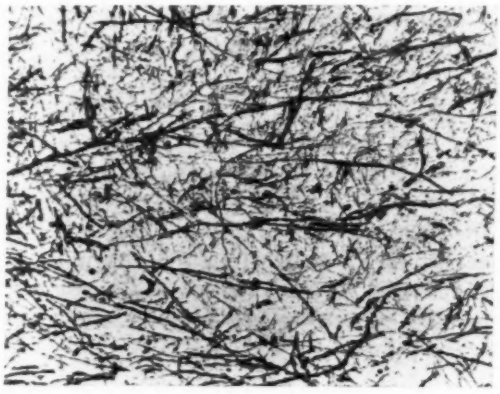

FIG. 13.—Higher magnification of fig. 12. × 120.

and, as pointed out by Foix and Nicolesco, may be found under normal conditions. With regard to the globus pallidus the number of cells was not appreciably reduced in any of the cases. The average count per field lay between the normal figures, i.e., forty and fifty. Four out of the eight cases showed a count between forty and forty-two cells per field ; it is possible that in these cases there may have been a small reduction in the actual number of cells. For the most part the cells of the globus pallidus appeared healthy, but not uncommonly a few appeared shrunken or showed chromatolysis. This region of the brain is difficult to fix properly and a good Nissl preparation is not always obtained, therefore at times it is difficult to assess certain alterations that may be found in these cells. The vessels in the globus pallidus showed the same changes as did those of the putamen, namely, an occasional discrete

perivascular lymphocytosis and dilatation of the perivascular space. In three of the nine cases deposits of iron salts were found in vessel walls in the anterior half of the globus pallidus; one of these cases (No. 3) also showed numerous deposits of iron in the form of globules. In a previous paper, such deposits in the globus pallidus were described in several cases of acute encephalitis, in one case of Parkinsonism and in several miscellaneous conditions. An opinion was expressed that such changes were unimportant from the point of view of symptomatology. The relative infrequency of these deposits in the present series of cases would seem to support this view as does some recent work by Hurst [12] who examined the globus pallidus in a hundred brains, representing a wide range of diseases of the central nervous system, and found "calcification" of the vessels in as many as 50 per cent. of the cases. An increase in the number of glial cells in the globus pallidus was only noted twice and in each case it was slight.

The thalamus, beyond vessel changes, was normal in all the cases. In the lower sections through the basal ganglia, perivascular lymphocytosis was more marked as a rule than in the higher sections, especially around those vessels adjacent to the lateral ventricles; in addition some of these vessels were surrounded by a hæmorrhage. I agree with Hohmann that these are probably terminal. Of the various nuclei in the subthalamic region, three were especially studied, namely, the substantia innominata of Reichert, the corpus Luysii and the upper part of the red nucleus. The first named was normal in all the cases. The corpus Luysii appeared well developed and the cells were normal throughout the series. In two cases this nucleus showed a slight increase in its glial content. The same remarks apply to the upper part of the red nucleus. In these two cases gliosis was quite marked in the region of the zona incerta.

The mid-brain in every case was greatly altered. On cutting across this region in a case of Parkinsonism the zone normally occupied by the substantia nigra seems narrower, is poorly delimited and appears much paler as compared with the normal. This appearance is quite distinctive. The changes in the substantia nigra which were observed microscopically concerned the following elements: (1) cell structure; (2) glial cells; (3) blood-vessels; (4) nerve fibres. With regard to cell changes, the most constant feature was the marked outfall of cells. When compared with controls it was apparent that in some of the cases the cells had almost entirely disappeared. Here and there small groups of two or three cells remained, but these, for the most part, showed

chromatolytic changes. In other cases, the reduction in the number of cells was less striking, scattered islets containing small groups of cells remaining, some of which contained normal cells. But in no case did the cells of the substantia nigra nearly approach the normal number. Clinically every case showed bilateral rigidity; pathologically in every case the substantia nigra was affected on each side, though in one or two instances the reduction in the number of cells was more marked on one side. In six of the cases, cell destruction was apparent throughout the substantia nigra; in two cases it was more marked towards the inner half of the zona compacta. As a result of the destruction of the cells, quantities of pigment were observed lying free in the parenchyma; some of it could be traced to vessel walls whence it had been carried by phagocytes. In persons under the age of 20 the scattered pigment will be scanty owing to the fact that at this age the intracellular pigment is normally small in amount.

An increase in the number of glial cells was present in every case in the region of the substantia nigra and was a marked feature except in a solitary case. The commonest glial cell observed was one which had a large oval pale nucleus containing chromatin dots, and which showed scanty processes. Small and large astrocytes with abundant processes were, however, relatively numerous, as were neuroglial cells with rod-shaped nuclei. This process of gliosis was practically confined to the substantia nigra and the periaqueductal grey matter in the mid-brain and pons, being less marked here, however, than in the substantia nigra. Neuroglial fibres were especially plentiful in the region of vessels. Anglade [1] lays considerable emphasis on this point.

With regard to the vessels, marked cuffing such as is met with in the acute stage was present in two of the cases; in both of these death had taken place within six months of the acute attack. In Case No. 1 in which the disease had been present for eighteen months the perivascular lymphocytosis was less marked, but was more evident in the region of the substantia nigra than elsewhere. Deposits of pigment in the vessel walls with thickening of the adventitia were also found. An important and nearly constant finding concerned the capillaries which were present in excessive numbers.

The nerve-fibres in Weigert-Pal preparations showed definite alterations in their myelin sheath. In some cases there appeared to be a thinning out of the fibre network; in others the fibres appeared numerous but many were interrupted in their course; the myelin sheath appeared as a series of beads; other fibres were broken across, the ends terminating in a large bulbous swelling (see figs. 11, 12 and 13).

The pons, in nearly all the cases, showed a gliosis in the grey matter underlying the aqueduct of Sylvius; this process spread out laterally and often involved the locus cœruleus. In two cases the cells of the locus cœrulus were almost entirely destroyed on one side. Clinically neither of the cases showed signs more marked on one side as compared with the other. In some of the remaining cases, depigmentation and chromatolysis of some of the cells of the locus cœruleus were met with. The lower pons and medulla were, in all the cases, normal. The cerebellum, and in particular the dentate nucleus, appeared normal throughout the series, except for an occasional discrete perivascular lymphocytosis.

Most of the changes which have been described above in connection with the substantia nigra have been noted by the majority of workers on this subject and as stated at the commencement of this paper there seems to be an almost complete unanimity of opinion as to the manner in which the substantia nigra is affected in Parkinsonism.

I am greatly indebted to Professor A. J. Hall for his kindness in placing the material and notes of five of the cases at my disposal.

Summary.

(1) An account of the literature dealing with the anatomo-pathology of post-encephalitic Parkinsonism is given. There appears to be a consensus of opinion that the substantia nigra is constantly and severely affected, and although a few observers do not attribute the Parkinsonian syndrome to a lesion of the substantia nigra, *per se*, the majority seem to hold this view.

(2) A short account of our present knowledge regarding the anatomy of the substantia nigra is given and some recent experimental work bearing on the subject is reviewed. It would appear that this nucleus is connected with centres below and above it, of which the globus pallidus is the best known.

(3) A description of the histological findings in a case of acute encephalitis is given. By comparing the distribution of the lesions in the acute stages of the disease with those found in the Parkinsonian syndrome, it would seem that although the inflammatory process is widespread initially, affecting particularly the basal ganglia, subthalamic region and mid-brain, yet, whatever phase of the disease is considered, it is the mid-brain, and especially the substantia nigra, which as a rule bears the brunt of the disease.

(4) The histological findings in eight cases of Parkinsonism are

described. From a study of these cases it would appear that the only group of cells which is constantly affected in this disease is that of the substantia nigra.

(5) Subacute inflammatory changes were present in all the cases, being especially marked in the mid-brain, even when the duration of the illness had exceeded twelve months. The persistence of the infective process would explain the latent period that may occur in some cases between the initial illness and the onset of Parkinsonism, it being supposed that the substantia nigra was little affected in the first instance.

(6) Gliosis in the region of the substantia nigra was especially marked in those areas denuded of cells. It was also apparent, though in a less degree, in the periaqueductal grey matter.

(7) The basal ganglia and in particular the globus pallidus showed no noteworthy changes.

(8) The locus cœruleus was markedly affected on one side in three of the cases. The normal cells of this nucleus do not resemble those of the substantia nigra except in regard to the pigment, being much rounder; presumably, therefore, these nuclei differ in their functional activity. This would suggest that a lesion of the locus cœruleus does not result in any of the motor phenomena characteristic of the Parkinsonism syndrome, but that it might be responsible for some of the symptoms attributed to the vegetative system.

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EXPERIMENTAL STIMULATION OF THE CEREBELLUM.

BY THE LATE DR. R. H. CLARKE.

[The late Dr. R. H. Clarke collaborated for several years with Sir Victor Horsley in his experimental researches on the nervous system. It was Clarke who designed and constructed the stereotaxic instrument described in their article on the cerebellum in this journal in 1908 [5], by means of which they were able either to stimulate or to produce local lesions in any portions of the brain they wished. It was chiefly in their experiments on the cerebellum between the years 1903 and 1910 that they employed this instrument. Their methods and some of their conclusions are described in what was obviously intended to be a preliminary communication [5], but owing to reasons referred to here by Clarke the great bulk of their work has never been published.

After Clarke's recent death several chapters intended for a book or monograph on the anatomy and physiology of the cerebellum were found among his papers. Unfortunately none of these chapters were completed for publication, probably owing to his prolonged ill-health. The following pages, taken from one of these chapters, seem worthy of publication as they contain important observations, and especially as these lead to a conclusion at variance with the opinion expressed in the article of 1908, which Horsley and he concluded with the following paragraph:—

"Perhaps the most concrete result of our method of investigating the cerebellum is the revelation of the motor functions of the intrinsic cerebellar nuclei as demonstrated by excitation. As already stated, the negative result of bipolar excitation of the cortex cerebelli gradually changes into a positive effect as the needle passes forwards among the axones of the Purkinje cells running to the nearest nucleus until the stimulus is directly applied to the nucleus itself, or to the paths and tracts issuing from it, when the result becomes maximal with even a very weak excitation" [5].]

A FEW investigators who have stimulated the cerebellar cortex with electrical currents elicited responses in various muscles, and considered they obtained proof of localized motor centres in the cortex. But, in the accounts I have seen, they merely applied the electrodes to the cortex and increased the strength of the current till they got a response. They did not record the strength of the stimulus; they did not compare the relative excitability of the cortex and the deeper parts, especially of the nuclei, nor of different regions of the cerebellum, such as the upper part and the floor. Nor do they mention any precautions to test or prevent escape of current to neighbouring structures, as the paracere-

bellar nuclei, or to determine whether the effective impulse was not really generated there by conduction. These are indispensible precautions, and when omitted deprive the results of practical value.

Horsley and I worked for eight years at this subject. We carried out systematic stimulation of the cerebellum in a great many animals of different species, and adopted every plan we could think of to control and test the escape of stimuli to neighbouring centres.

Some of our experiments have been described in our two papers [4], [5], but the bulk of them have not been published. By the time we thought we had collected sufficient material, Horsley had become immersed in other work, and he had no time to digest our material. He hoped to retire from practice before long and devote his time to working up the material, of which he had a prodigious quantity, in addition to that in which we collaborated, but his untimely death in 1916 in Mesopotamia closed his brilliant career and valuable life. At present I have only got our notes for one year, 1906, but I think a few abstracts from these notes will be instructive in illustration of our results of stimulation of the cerebellum.

Stimulation Experiments.

In that year (1906), besides experiments on other animals, we stimulated the cerebellum in thirty-two monkeys and three armadillos. I have chosen the latter because they represent a simple type of animal and the method was simple also: we had no frozen sections or charts to work by, so were only guided by anatomical landmarks, and we measured the depth of the insulated needle from the surface in millimetres; there is no topographical technique to explain and the description is simple.

In monkeys we employed for stimulation the double platino-iridium needles, insulated in fine glass sheaths ground to a point, described in our paper [5]; they were directed by my stereotaxic instrument from behind and penetrated the substance of the cerebellum easily, without producing any laceration. In the monkeys they were projected parallel with the nasion-inion line, which is represented by the longitudinal lines in the ruled squares, and the distance was measured from the posterior surface of the cerebellum; the height was estimated from the obex, corresponding to the spur of the pyramid. Subsequently, we used the line known as Reid's line, measuring the height from this, and the longitudinal measurements were made from the frontal zero

plane. These lines are shown in the photographs, the direction not differing very much from that adopted. We began with the former method and were still employing it when these experiments were made.

I have analysed the records of experiments on twenty-six monkeys and have adopted a graphic method by which the principal results can be seen at a glance. On an average we made between 50 and 100 observations on each animal, perhaps 1,500 altogether; of these I have selected every instance in which a response was elicited by 100 or less

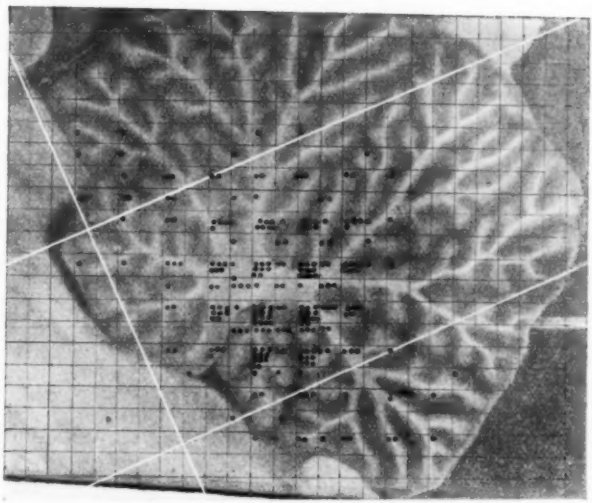

FIG. 1.—The results of stimulation of the cerebellum in twenty-six *rhesus* monkeys. The dots represent the points, projected on to the mesial sagittal plane, from which movement of the head or eyes, or of both, were obtained by stimulation with 100 units or less on Krönecker's coil.

on Krönecker's coil. I can give the exact situation of each of these stimulations and show them in the following way: I have photographed two sections of the monkey's cerebellum, one, a medial sagittal, the other a frontal section through the nuclei (postfrontal lamella viii) (3). I have ruled them with fine lines into square millimetres and enlarged them five diameters. Then I have divided the recorded responses into three groups: (1) consisting of movements of the head and eyes; (2) of neck, face and shoulders; and (3) of the limbs, trunk and tail. Each group is recorded on two photographs representing a frontal and

sagittal section, the position of the point of the insulated needle, when the response was obtained, being indicated by a dot. Thus, all the stimulations of the twenty-six animals which elicited responses with a current of 100 or less on the coil, in the region indicated, are represented in two photographs of single sections in the sagittal and frontal planes. There are some defects in this method. If a glass plate 1 mm. thick were used to represent each lamella of the cerebellum, i.e., a slice 1 mm. thick, and the focal points from which reactions in each lamella were elicited were reproduced on a separate plate, and the whole built

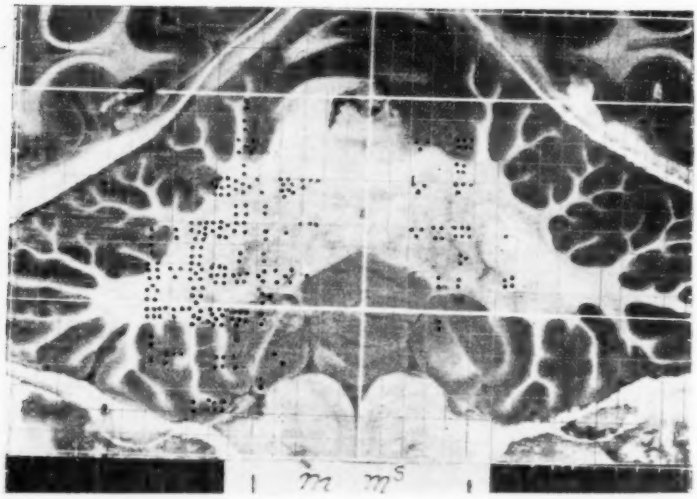

FIG. 2.—The points from which movements of the head or eyes, or of both, were obtained with 100 units or less on Krönecker's coil, projected on to a section in the frontal plane.

up side by side to form a glass reconstruction, the actual position of each point could be exactly reproduced. But, to represent them on paper, all the points on several lamellæ must be projected on a single section and therefore they cannot be made to allow for differences in the level of different parts of the cerebellum. But as most of the lamellæ which were stimulated were at no great distance from the median sagittal section, the error is not great, and by comparing the two planes a very fair idea is obtained of the sensitive area.

The much larger number of dots on the left side than the right does not indicate that the left side is more sensitive to stimuli than the

right, but that a larger number of experiments were made on that side. It often happened that we made an electrolytic lesion on one side, kept the animal for three weeks for degeneration to develop, and before it was killed under chloroform stimulated the normal side.

On the other hand, the number of points marked in the photographs of the three groups represent the relative frequency with which separate groups of muscles responded to stimulation of a number of points methodically scattered over a given area of the cerebellum. The response from the head and eyes is much the most frequent. We

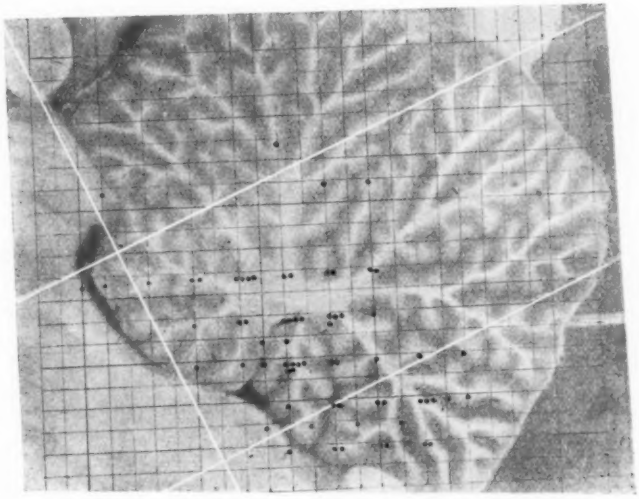

FIG. 3.—Description as in fig. 1. Movements of the head, neck and shoulders.

more often stimulated the lamellæ near the medial sagittal plane than outlying ones.

We usually began with stimulation of the cortex, increasing the strength of the stimulus till we obtained a response; the needle was then advanced, 2 mm. at a time, into the cerebellum, and the stimulation repeated at each interval. The points of the double needle were separated by about 1 mm. and usually the current was passed between them (short arc, or bipolar stimulation). But there is a switch on the instrument by which one of the needles can be cut off, and then the metallic termination, or "stop" of the needle holder, which is in contact with the surface of the cortex, can be made the indifferent electrode

or "live stop," the current then passing from the point of the focal needle to the surface, along the course of the needle. Or, a third alternative could be adopted, by switching off from the live stop to the frame of the instrument, which is in contact with the head at many points all round it; the current then passed from the focal point to all these points of contact with the cranium. It is an advantage to be able to employ all these arrangements without any loss of time, as they throw some light on the escape or conduction of stimuli. Sometimes by making these changes different results are obtained, and by com-

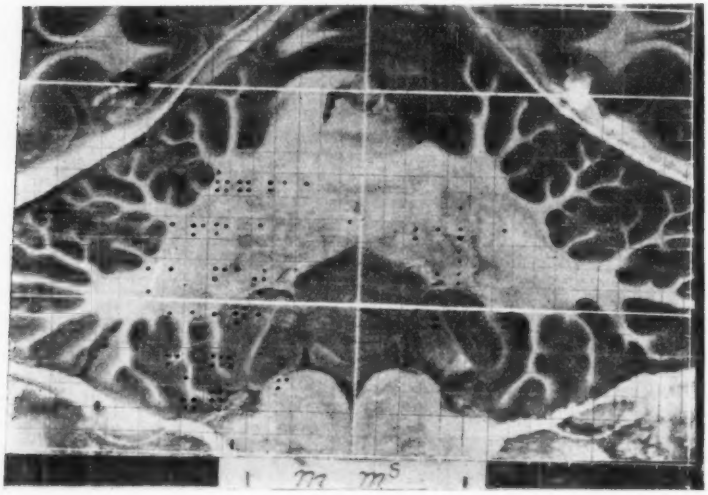

FIG. 4.—Description as in fig. 2. Movements of the head, neck and shoulders.

paring them the direction of escape and the nuclei involved are made evident.

We employed a Krönecker's coil, always the same instrument, for all the experiments. The degrees into which it is graduated do not profess to be absolute measurements of current, but the proportion is believed to be correct and, as far as we could judge, it appeared to be so. It served our purpose very well as we wished to ascertain the relative, not absolute, excitability of different parts. The current was generated by two dry cells.

Whenever we obtained a reaction we particularly wanted to note, we always made a pin-head electrolysis at that point, so that we could

recognize it in sections afterwards. This could be done very quickly: by opening or shutting two or three keys the coil was cut out and the needles brought into a circuit of a dozen dry cells with an ammeter and a rheostat, by which a constant current of from 1 to 5 milliamperes could be passed between the needles; we usually began with a strength of 1 milliampere, and raised it. At make and break there was generally a much more powerful response, often confused and widely conducted, than that obtained by the faradic stimulus. Of little value by itself, it sometimes afforded additional information on the question of escape of

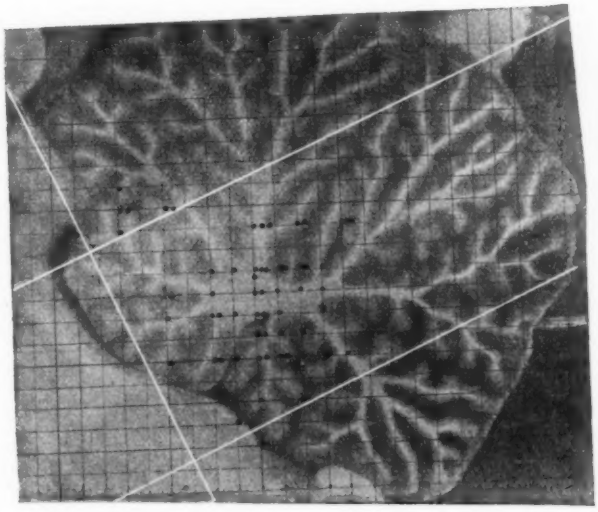

FIG. 5.—Description as in fig. 1. Movements of the limbs.

current and paths of conduction. We employed other control tests which I need not describe here; I only wish to point out that the question of conduction to other centres was under continual consideration in all our experiments, and it certainly ought to be.

On the cortex a strength of current of from 1,000 to 1,500 or more units on the coil was necessary to obtain responses, and in the intervening area movements were elicited by currents of gradually diminishing strength. By the time a point was reached where a response was obtained with 100 or less on the coil, the end of the stimulating needle was in the neighbourhood of the central nuclei, often in the dentate.

Movements of the head and eyes were most commonly induced from here.

It is evident on examining the photographs that the sensitive area, where responses can be obtained with weak stimuli, is in the neighbourhood of the nuclei and includes but is not restricted to them. It corresponds to the floor of the cerebellum, the roof of the fourth ventricle and a region that contains tracts which form paths of least resistance to electrical currents. It will be seen that though reaction of other parts of the body than the head and eyes are less frequent, they are obtained

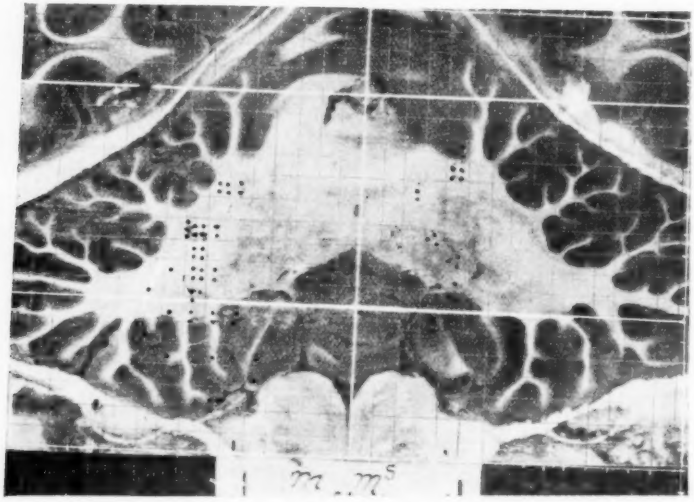

FIG. 7.—Description as in fig. 2. Movements of the limbs.

over much the same sensitive area. There is no suggestion of anything like localized centres for these different groups of muscles: all responses are obtained from points where stimuli are easily conducted to paracerebellar nuclei.

A consideration of the small size of the cerebellum and bulb in the monkey and cat; the relations of the fourth ventricle which is filled with such an excellent conductor as the cerebro-spinal fluid; the proximity to the floor of the cerebellum of the nuclei of the motor cranial nerves and of Deiters' nuclei, and the connection through the superior peduncle of the cerebellum with the mid-brain, makes it obvious how easily stimuli can be conducted to the brain-stem, and

I am convinced they are conducted in every case where responses, in the form of muscular contractions, are obtained.

We carried out stimulation experiments on all parts of the cerebellum with the precautions I have mentioned, and we found that in all animals the sensitive area includes the floor and the nuclei of the cerebellum and important neighbouring tracts. From this area muscular contractions can be obtained in every part of the body, but anything approaching a localization within it is determined only by the proximity, measured by distance or resistance to the passage of electrical currents, of some paracerebellar structure, which I believe was the actual source of each impulse which elicited a response.

The chief conclusions that may be drawn from these experiments are: (1) That the cortex of the cerebellum is inexcitable, in the sense of originating impulses that act directly on particular groups of muscles. (2) The only part of the cerebellum sensitive to electrical stimulation is the region of the central nuclei and the floor of the fourth ventricle, but the reactions obtained from here are due to the spread of the electrical current to neighbouring bulbar and mesencephalic structures, or to its conduction by paths of least resistance to parts of the nervous system with which the cerebellum is closely connected.

The most frequent responses to stimulation of the cerebellum in all the animals we employed were movements of the head and eyes. This was often a conjugate movement, but it may be of the head only, or of eyes only, or of only one eye. It was generally to the same side, but sometimes to the other, and all movements of the eyes may be observed occasionally. These movements do not, however, resemble those due to the direct response of a motor centre to a stimulus; they are slower and more deliberate, and are probably secondary effects of impulses conveyed to the brain-stem.

I will now give some extracts from my notes of the results of stimulation in the armadillo.

Armadillo No. 1 (*Dasypus villosus*).

(1) Stimulation of cortex, left side of vermis, sixth folium from below (there were nine folia to the top of the vermis, therefore this was the junction of middle and upper thirds). No result up to 1,000 on the coil, then slight raising of the eyes.

(2) Stimulated both sides of cortex of vermis at various points from above downwards; with 1,250 on the coil, both eyes raised and turned slightly towards side stimulated. As we approached the pyramid, escape of current to the trapezius (accessory).

(3) All down outer border of paramesian sulcus, i.e., on white substance, both sides; with 1,000 on the coil, retraction of both eyes, bending of head downwards; escape to trapezius as we came down.

(4) Electrodes entered 5 mm. deep into the upper part of left paramesial lobe. No result up to 500 on the coil, then the left eye moved slightly up and to the left. Shrugging of the left shoulder and protraction of the left fore-limb.

(5) Middle of third folium from below, left paramesial lobe 5 mm. deep, 500 on coil: the left eye moved down and to the right.

(6) Left of sixth folium of vermis from below, half way between middle line and paramesial sulcus, 5 mm. deep; 500 on the coil gave no result, 1,000 on the coil produced cog wheel retraction of both eyes and then the left eye moved up and the right eye down; twitch of both facials, snout turned to the right. Electrodes advanced to 8 mm. deep, with 500 on the coil no effect, 1,000 on the coil evoked retraction of the left eye and protraction of the right, then retraction of both, followed by retraction of the right and protraction of the left; shrug of the right shoulder.

These stimulations were comparatively superficial; strong currents were required to give any response and these, when obtained, were exceedingly irregular and probably all conducted, some unquestionably to Deiters' nucleus and the accessory nerve nucleus.

Armadillo No. 2.

(1) 9 mm. to the left of the median line, 10 mm. above the level of the obex; no response obtained up to 4,000 on the coil, then the right eye moved forwards.

(2) Same place, electrodes entered 5 mm. deep, coil 200: the left eye moved forwards and downwards, the right eye forwards and upwards.

(3) Same place, electrodes 10 mm. deep, coil 100; the left eye turned up.

(4) Cortex 7 mm. to the left of the median line, 10 mm. above the obex: no response up to 4,000 on the coil, then the right eye moved very slightly forwards. Same place, but electrodes 5 mm. deep, coil 100; the left eye turned upwards and the right eye forwards. 10 mm. deep, coil 100; the left eye turned upwards and forwards, the right eye the same.

(5) 5 mm. to the left of the median line, 10 mm. above obex, electrodes 5 mm. deep, coil 100; the left eye moved up, the right eye forwards and slightly downwards.

(6) Same place, 7·5 mm. deep, coil 100; the left eye turned upwards and forwards, the right eye downwards.

(7) Same place, 10 mm. deep, coil 50; left eye moved up, with very marked and very protracted jerking retraction. All four limbs flexed and exhibiting jerking movements. Stimulation repeated in the same spot, coil 20: the left eye turned up, flexion of the right hock and foot.

These observations show the great difference in strength of current required to elicit responses when applied to the cortex and to deeper parts. The responses were irregular and probably due to conduction of the current. In the later stimulations the electrodes were very near Deiters' nucleus which obviously reacted; the stimulus was only 20 on the coil, as compared with 4,000 on the cortex. It shows how misleading it may be to use currents without measuring them in some way.

We stimulated a number of regions in this animal; in the region of the dentate nucleus, with stimuli of about 50 on the coil, we got more regular responses of the eyes, and generally if one went up the other went down; one forwards, the other backwards; one clockwise, the other anti-clockwise. These movements of the eyes are very common in the armadillo and other animals with divergent eyes. The clockwise and anti-clockwise rotation is not a reverse rotation, as it appears; the eyes are rotating in the same direction, but the observers must regard them from opposite points of view; the same thing happens if the wheels of a cart moving in the same direction are regarded from the opposite sides. In this animal clockwise rotation was obtained by introducing the electrodes 1 mm. to left of middle line, 8 mm. above obex, to a depth of 10 mm. and with a current of 50 on the coil. I discussed these eye movements in the armadillo in a previous paper [1].

Armadillo No. 3.

In this animal we did not waste time over the cortex, but began by introducing the electrodes 5 mm. deep in each observation.

(1) Vermis, electrodes 1 mm. to the left of the mid-line, 10 mm. above obex, 5 mm. deep: no effect obtained to 3,000 on the coil, then twitch of the face.

(2) Ditto, the same result, but 4 mm. higher (above obex) at about the top of the vermis, 5 mm. deep, no response was obtained.

(3) Paramesial lobe, 8 mm. to the left of the mid-line, 10 mm. above obex 5 mm. deep, no result up to 2,000 on the coil; then the left eye moved down and slightly forward, the right eye backwards.

(4) Same, 2 mm. lower, i.e., 8 mm. above obex, 5 mm. deep; no effect to 1,000 on the coil, then the left eye moved down, the right eye upwards, the head to the left; extension of the left wrist and right knee.

(5) Same, 6 mm. above obex, 5 mm. deep, no movement up to 1,000 on the coil, then the head turned to the left, the left eye moved down and the right eye up; extension of the knees, chiefly of the right, and flexion of both elbows.

(6) Same, 4 mm. above obex, 5 mm. deep, 100 on the coil; the head turned well to the left, the left eye moved slightly forwards, the right slightly backwards; flexion of the left elbow and extension of the right; extension of both knees; ventral flexion of the tail and slight deviation to the right.

In each of these six observations the electrode was 5 mm. deep from the surface. The responses were movements of the eyes, due to conduction of the stimuli to the intrinsic nuclei, especially the dentate, and movements of the limbs through Deiters' nucleus. The latter is a most important nucleus in the armadillo and all paths seem to lead to it. It will be seen that towards the upper part of the cerebellum movements were elicited with difficulty and required strong currents, but as the floor of the cerebellum was approached responses were elicited with weaker stimuli, and close to the floor of the fourth ventricle, 4 mm. above the obex, in the region of the large fastigio-cerebellar and other tracts and of Deiters' nuclei, movements were obtained with very weak stimuli.

All these observations were made on the left side; identical effects were obtained on the right side.

(1) The vermis, 2 mm. to the right of the mid-line, 14 mm. above the obex and 5 mm. deep; no response was observed till the current reached 1,000 on the coil, then flexion of the right elbow occurred.

(2) Same plane, 10 mm. above the obex and 5 mm deep, 1,000 on the coil, rotation of the head and eyes to the right, right ear approximated to the right shoulder, flexion of the right elbow and extension and abduction of the left fore-limb.

(3) Same plane, 8 mm. above the obex, coil 500; movements of the right eye downwards and forwards, of the left upwards and backwards; right ear to the right shoulder, extension of the right elbow and flexion of the left; extension of the right knee.

(4) 6 mm. above the obex, 5 mm. deep, 50 on the coil; all the same movements as in the last experiment, but they were stronger and accompanied by rotation of the whole body to the left, extension of the right elbow and flexion of the left, and flexion of the right hip.

(5) 4 mm. above the obex, 25 on the coil; very slight movements of the eyes, the right downwards, the left upwards, 50 on the coil: the same effects but stronger; 100 on the coil evoked more vigorous movements of the eyes and slight flexion of both elbows; 200 on the coil produced contraction of the right side of the face and strong movements of the eyes.

(6) Surface of the right tuberculum acusticum, 100 on the coil; the right eye moved forwards, the left was retracted violently; slight extension of the left wrist and flexion of the right elbow.

(7) Deiters' nucleus, 25 on the coil; flexion of the right elbow, the left eye moved upwards and the right downwards and forwards.

These responses were very similar to those obtained on the left side and the same remarks apply. It is interesting to see that with a weak stimulus (100 on the coil) applied to the tuberculum acusticum movements of the limbs resulted; no one would suggest that the tuberculum acusticum is a motor centre for the limbs, so the current obviously spread to other centres in the grey matter. A similar response was elicited on stimulating Deiters' nucleus with 25 on the coil. On reviewing all these results it seems hardly possible to doubt that they were produced by conduction of the stimuli to motor centres in the neighbourhood of the cerebellum.

A comparison of the few observations on the armadillo here described with the synopsis of the experiments on the monkey shows them to be inconsistent, as far as they go, with the existence of motor areas of any kind in the cerebellum, and least of all in the cortex where the strongest stimuli were always required to elicit muscular movements. The very large number of experiments which we made on various animals entirely supported the same conclusion; there were no exceptions.

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[3] *Idem, idem.* "Atlas of Photographs of the Frontal Sections of the Cranium and Brain of the Rhesus Monkey," *The Johns Hopkins Hospital Reports*, Special Volume, Baltimore, 1920.

[4] HORSLEY, V., and CLARKE, R. H. "On the Intrinsic Fibres of the Cerebellum, its Nuclei and its Efferent Tracts," *Brain*, 1905, **28**, 13.

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Proceedings of the Section of Neurology of the Royal Society of Medicine.

President—Sir JAMES PURVES-STEWART.

Clinical Meeting held at the West End Hospital for Nervous Diseases, on Thursday, November 11, 1926, at 8.30 p.m.

An Incomplete Form of von Recklinghausen's Disease.

By Dr. MACDONALD CRITCHLEY.

THE patient, a girl, aged 11, came under treatment for an epileptic attack which occurred three months ago. Eighteen months previously a subcutaneous tumour (neuro-fibroma) had been removed from the right forearm.

There is a very definite degree of pigmentation over the trunk, consisting in numerous lentigines and *café au lait* patches upon a uniformly stained background. No skeletal changes. No neuro-fibromata. No endocrine or psychical abnormalities. Nystagmus on lateral ocular deviation.

The family history is negative except for a sister with scoliosis.

Dr. PARKES WEBER pointed out that such a case should be referred to as an early, not as an incomplete form, of von Recklinghausen's disease, as the majority of them develop into the typical disease. He referred to a girl, then aged 15, whom he had shown at the Dermatological Society in 1905, with pigment similar to that present in Dr. Critchley's case. In the present year she is a characteristic example of neurofibromatosis, and in addition to isolated tumours has a large plexiform neuroma on one side of the neck. The pigment is now the least prominent symptom. Other similar cases have been reported.

Dr. CLOAKE asked if a hypertrophic neuritis is ever associated with von Recklinghausen's disease, as a patient under his care who has pigmental spots complains of paræsthesiæ in the limbs and the ulnar nerves are thickened, but there are no tumours.

Hemiplegia supervening upon an Atrophic Limb.

By Dr. MACDONALD CRITCHLEY.

The patient had an attack of acute anterior poliomyelitis during childhood, which left him with an atrophic paralysis of the right shoulder-girdle and upper arm-muscles.

Twenty years ago he had a stroke giving rise to a right hemiplegia.

Reflex contractions can now be elicited with ease in the atrophic muscle groups.

Dislocation of Second Cervical Vertebra with Slow Onset of Quadriplegia.

By Dr. ARTHUR J. DAVIES.

Five months ago the patient was rendered unconscious in an accident and sustained a dislocation of the second cervical vertebra. The patient had no pain after recovering consciousness and walked about for a period of eleven weeks. He then resumed work for another two months.

Eight weeks ago he began to feel pain and stiffness in his feet, which spread in the course of two weeks to the thighs.

Three weeks ago, stiffness and aching started in the shoulders and extended down to the finger-tips.

The present condition is one of spastic quadriplegia, with exaggeration of the tendon-jerks; abdominal responses present; plantars extensor in type. No sensory loss. No sphincter disturbance. No limitation of head and neck movement, and no rigidity. Some tenderness over C 3, 4 and 5 spines.

A skiagram reveals a forward displacement of the body of C 2 on C 3. There is some new bone formation bridging over the second intervertebral space.

Dr. IRONSIDE suggested that the spinal symptom might be due to a serous meningitis. The cerebro-spinal fluid obtained by lumbar puncture was normal: a cisternal puncture has not been done.

Dr. YEALLAND inquired of the condition of the respiratory muscles, as with such a high spinal lesion it is surprising that the patient breathes as easily as he does.

Dr. HOLMES suggested that the lesion might be a cavity formation within the cord, such as is frequently observed after spinal concussion. In some cases he had observed the cavities developed some weeks after the trauma. In one case at least a spontaneous recovery had taken place.

Dr. ADIE said the chief interest of the case lay in the fact that spinal symptoms began to develop only eleven weeks after the injury. He referred to a similar case in a woman who fell a considerable height from a window; at first she presented no nervous signs, but later developed a paraplegia. After death an excess of fibrous tissue was found around the cord, compressing it.

Cases from a Family affected with Leber's Disease.

By Dr. REDVERS N. IRONSIDE.

Case 1.—C. F., aged 53 (umbrella coverer). Onset sudden *nine months ago*. For a few seconds things seen with the right eye "seemed faded." The sight improved but has never been perfect since. There has been gradual failure of vision in both eyes. Newspaper type, he says, looks like Yiddish type. Sees better in a dimly lighted room. Vision best at 6 a.m. and is said to be poor in the afternoon. No previous serious illness apart from typhoid fever when aged 21.

On examination.—Right vision $\frac{6}{60}$, left vision $\frac{6}{36}$. Fields of vision show bilateral central scotomata and general constriction. Right optic disc white all

over. Left optic disc similar appearance, possibly not so intense. X-ray of skull shows a normal sella.

Case 2.—M. C., aged 55 (sister of above). Onset when aged 19, suddenly, while working in a restaurant. When the vision grew dim she dropped a glass on the counter and was unable to see the pieces in front of her to pick them up. Three years later she was able to read fairly large print. The left eye has always been less affected than the right. When she shuts the left eye there seems to be a central blurring of her vision.

On examination.—Right vision $\frac{6}{60}$, left vision $\frac{6}{60}$. Fields of vision reveal a central scotoma in left eye. Right optic disc: pale, macular stippling. Left optic disc: greyer than normal.

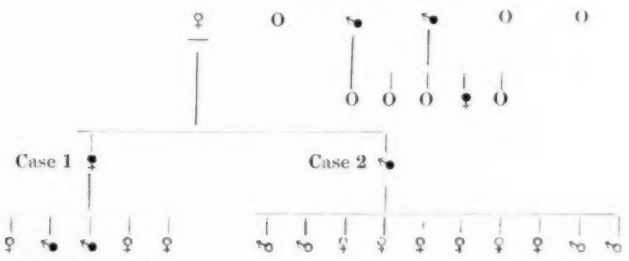
Case 3.—S. C., aged 27 (tea-taster), son of M. C. Sudden onset *eight months ago*, about March 5, 1926. Failure of vision was noticed first in the right eye, then in the left. The centre of the field of vision was most affected in each eye. No serious illnesses.

On examination.—Right vision $\frac{6}{36}$, left vision $\frac{6}{18}$. Visual fields show a central scotoma in the right eye and general constriction. Right optic disc: high coloured, edges blurred, vessels full, swelling + 1 D. Left optic disc: edges blurred, disc high coloured, swelling + 1 D. Appearances consistent with a fairly far-forward retrobulbar neuritis. X-rays of skull show a normal sella turcica.

Case 4.—G. C., aged 29 (warehouseman), son of M. C. Onset suddenly and without pain, when aged 16. Failure of vision was worse in the right eye. The mistiness of vision is mostly in the centre of the field of vision, especially in bright sunlight. Looks at objects obliquely to see them clearly. Acuity of vision decreases when he is run-down. No previous illnesses of note.

On examination.—Right vision $\frac{6}{60}$, left vision $\frac{6}{60}$ (about). Fields of vision show central scotomata. Right optic disc: greyish-white pallor affecting right side of the disc; vessels of good calibre, disc edge clear. Left optic disc: similar appearance; lamina cribrosa not so conspicuous.

THE BEALE FAMILY.



Case 1 onset aged 53.
Case 2 onset aged 19.
Case 3 onset aged 27.
Case 4 onset aged 16.

These cases are distinctly related to another family (Clayton) which is also affected with Leber's disease. The different ages at which the symptoms set in, in different patients, is interesting. A papillitis such as is present in Case 3 is known to occur in the early stages of Leber's disease, but is not frequently seen. None of these cases present other neurological symptoms, and the X-rays of their skulls show normal sellæ turcicæ.

Dr. CLOAKE pointed out that in two of the cases the symptoms had developed after dental extractions, and suggested that the visual disturbance might be due to a toxic or infective retrobulbar neuritis, as a result of special familial vulnerability.

Mr. LINDSAY REA thought the most satisfactory pathogenesis of these cases was a swelling of the pituitary compressing the optic nerves, as Mr. Herbert Fisher has suggested. He referred to a progress of the blindness in some cases.

Dr. HOLMES pointed out that there were many arguments against the pituitary hypothesis. In the first place the symptoms almost invariably develop rapidly, and in some patients a considerable recovery of vision takes place. Further, in his experience, the visual condition usually becomes stationary after an acute onset; a progressing blindness must be very rare. It is difficult to see how a swelling of the pituitary could produce a retrobulbar neuritis of acute onset that did not progress. Further, a papillitis, such as was present in Case 3, could scarcely be expected to result from an enlargement of the pituitary unless associated with signs of considerable intracranial pressure, and headache is certainly a rare symptom.

A Case of Postural and Stereognostic Loss in the Upper Extremities.

By Dr. C. P. SYMONDS.

R. C., male, aged 54, works manager, complains of numbness in his left hand of five years' duration and a similar feeling in his right hand for twelve months. Has felt listless and run down the last year.

Past history.—Beyond an occasional "septic throat" has been quite well. Alcohol and tobacco in moderation.

Present illness.—Five years ago began to notice his left hand felt cold and was numb. In cold weather it "went purple" in colour. He dropped articles out of his left hand. He has difficulty in finding his pocket and distinguishing things in his pocket. The condition has been persistent and progressive, but is always worse in cold weather. The last twelve months a similar condition, but in a milder degree, has become manifest in his right hand. He can write, but feels clumsy and awkward. The last two years, on falling to sleep and whenever he relaxes his muscles, his whole body gives "a big jump." No visual or sphincter disturbances. No pain.

On examination.—Mentally normal. Bilateral ptosis with overaction of frontalis. The right naso-labial fold is not so well marked as the left, and the right corner of mouth not quite so well retracted as the left. Otherwise the cranial nerves are normal.

The power of both arms is quite good and tone normal. The left hand is slightly purplish in colour and usually colder than the right. Finer movements are awkwardly performed by the left hand. Over the left hand and to above the wrist, perception of heat and cold is slightly impaired. In the right hand the impairment extends only as far as the metacarpo-phalangeal joints. Sense of position is grossly impaired in the left hand, especially in the distal joints of the fingers, and is fairly good at the wrist. Right hand: no gross impairment. Vibration sense is impaired in left hand and wrist, slightly in the right. There is complete astereognosis in the left hand.

All the superficial and deep reflexes are normal in character. The power and tone of legs normal. Gait normal.

The cerebro-spinal fluid is clear, colourless and contains no cells. Total protein, 0·025 gr. Nonne-Apelt, negative. Pandy, negative. Lange, no change in any tube, and the Wassermann reaction is negative in the blood and cerebro-spinal fluid.

Dr. SYMONDS said he presented this case to obtain an opinion on the nature of the lesion. The ptosis, the postural loss and the astereognosis in the hands suggest a cervical tabes, but the normal cerebro-spinal fluid, the negative Wassermann reaction and the intact reflexes go against this diagnosis. He assumed the existence of two separate lesions in the dorsal columns of the cord. It might possibly be a case of disseminated sclerosis, but if so the ptosis would have to be regarded as a congenital defect.

Case of Syphilitic Encephalitis.

By Dr. C. P. SYMONDS.

J. C., male, now aged 47, first attended hospital December 3, 1924, having had three generalized epileptic seizures on the previous day. There had been no headache or other symptoms. He had had twenty-five years' service in the Regular Army, and admitted syphilis eighteen years previously. Apart from this he had had no serious illness. There was no previous history of any epileptiform attack.

On examination the mental state and speech were normal. The pupils were small and irregular, and reacted sluggishly to light and on accommodation. Old-standing middle-ear deafness was present on both sides. Apart from this no physical signs of disease could be detected. The Wassermann reaction was strongly positive in blood and spinal fluid. The specimen of the latter sent for chemical and cytological examination was unfortunately lost. He was given mercury and iodides by the mouth, and novarsenobillon intravenously in weekly doses, rising from 0·45 grm. to 0·9 grm., until 5 grm. had been given; six weeks later a further course of 5 grm. was given in the same way. The mercury and iodides were continued throughout. He had no more fits or other symptoms. In June, 1925, the physical signs were unchanged. The Wassermann reaction in the spinal fluid was weakly positive with 1 cell per cubic millimetre and 0·04 per cent. protein. He has since attended annually for a short "prophylactic" course of four weekly doses of 0·9 grm. novarsenobillon, with mercury

and iodides by the mouth. There has been no recurrence of the fits, no further development of symptoms or physical signs. He has been working regularly as a wharf hand throughout the whole period under review.

The first diagnosis made in this case was general paralysis, but the marked improvement which has occurred negatives this.

Dr. SYMONDS considered the term "syphilitic encephalitis" preferable to "general paralysis," especially in cases seen in the early stage when exact diagnosis was often not possible. Syphilitic encephalitis would include both the benign and the malignant group. Arsenical injections seemed to him the best mode of treatment.

Dr. CARNEGIE DICKSON, as a pathologist, welcomed Dr. Symonds' suggestion to regard all these cases as syphilitic encephalitis, at least until definite symptoms of general paralysis developed.

Dr. FEILING insisted that general paralysis must be regarded as a clinical entity. He had seen many cases similar to that shown that evening, with sluggishly reacting pupils. Some recover under treatment, others develop general paralysis.

Dr. WORSTER-DROUGHT emphasized the importance of the Lange reaction in distinguishing parenchymatous from interstitial neurosyphilis.

Dr. SYMONDS recognized, of course, Dr. Feiling's claim for general paralysis as a clinical and pathological entity; his difficulty is to find a convenient name for early cases before definite symptoms have developed. He believed he had seen cases which clinically belonged to cerebral syphilis in which the Lange curve was of the paretic type.

Case of Combined Vascular and Parenchymatous Neuro-Syphilis.

By Dr. E. B. STRAUSS.

A. H., male, admitted to Hospital for Epilepsy and Paralysis, Maida Vale, October 21, 1926, suffering from aphasia and weakness of his right arm. Four months ago the patient noticed a feeling of heaviness in this arm. One month later sudden loss of speech and of power of right arm developed without loss of consciousness. On examination, marked aphasia of motor type, flaccid paresis of the right arm with reduced tendon reflexes; power in other limbs normal; flexor plantar responses; absent knee and ankle reflexes; fixed pin-point pupils. Discs normal, but marked arterio-sclerosis of the retinal vessels. Other systems show emphysema of chest and considerable dilatation of the right heart and ascending aorta, confirmed by skiagram.

Blood Wassermann negative. Cerebro-spinal fluid: clear and colourless; Wassermann reaction, negative; Nonne-Apelt, negative; total protein, 0·035 per cent.; cells per c.mm., 1·2; Lange, 1, 3, 3, 2, 1½, 0, 0, 0, 0; benzoin, 0, 0, 0, 0, 0, 0, 0, 2, 2, 000.

One point of interest in this case is that the patient is a Belgian, who before his illness spoke fluent English; now he converses only in a jargon of French and Flemish. He had recently seen general paralysis in a German who had lived forty years in England; as the disease advanced he lost English and spoke only in German.

Case of Juvenile Tabes with Rotatory Nystagmus.

By Dr. E. B. STRAUSS.

B. C., girl, aged 11, admitted to Hospital for Epilepsy and Paralysis, Maida Vale, complaining of impaired vision and involuntary movements of the eyes. Well-developed healthy-looking, intelligent child with no stigmata of congenital syphilis. Slight impairment of vision noticed five years ago following attack of scarlet fever. Nystagmus started three and a half years ago.

On examination, continuous fine rapid rotatory nystagmus unaffected by ocular movements; vision very fair in spite of marked refractive error. Primary optic atrophy. Absent knee and ankle reflexes.

Blood Wassermann negative. Examination of cerebro-spinal fluid: clear and colourless, pressure increased; Wassermann reaction, positive. Nonne-Apelt, negative; total protein, 0·040 per cent.; cells per c.mm., 95 (lymphocytes); Lange, negative; benzoin, normal.

Dr. ADIE regarded the presence of nystagmus in this case as a most interesting symptom. In his experience syphilitic disease of the nervous system is very rarely a cause of nystagmus; he believes Nonne is of the same opinion. The high refractive error which the patient has may be its cause here.

Mr. LINDSAY REA also emphasized the rarity of nystagmus due to syphilis. It is interesting that syphilis also seldom produces macular disease.

Dr. HOLMES pointed out that the nystagmus is of the optic rather than of nervous type. In his opinion it is not due to the involvement of any part of the nervous system. He observed that when the patient was asked to look at any object, she fixed by extra-macular vision, and testing by such rough methods as he could employ during the meeting showed definitely the presence of central scotomata. To him it seemed that the nystagmus was due to a long-standing defect of central vision. He recalled a similar case in a girl with juvenile general paralysis in which there were complete central scotomata, due probably to syphilitic retrobulbar neuritis.

Two Cases of Hypoglossal Nerve Involvement.

By Dr. C. WORSTER-DROUGHT.

Case 12.—Mrs. J. H., aged 37, complains of diplopia, giddiness, and wasting of the tongue.

History.—Nine years ago she had a seizure, consisting of sudden loss of consciousness—followed by loss of speech, diplopia and weakness of right arm and leg. Later, the tongue felt awkward. The arm and leg have gradually improved, but diplopia and the tongue condition have persisted.

Physical examination.—Pupils are equal and react normally; fundi normal. Pronounced internal strabismus of the left eye with diplopia: paralysis of left external rectus and apparently of superior oblique. Tongue on protrusion deviates to left and shows marked atrophy and weakness of left

half. Slight weakness of the left side of palate. Arm, abdominal and plantar reflexes are normal; knee- and ankle-jerks brisk, but equal. No inco-ordination.

Heart, lungs and other systems normal. Blood-pressure: 120 systolic, 75 diastolic. Urine, no abnormality. Blood: Wassermann reaction negative. Cerebro-spinal fluid: cells and protein, normal; Wassermann reaction negative.

Case 13.—Adolph W., aged 21. Complains of weakness of left arm and shoulder, wasting of the tongue, and occasional twitching of left side of face.

History.—The onset occurred about six months ago, with slight pain in left arm; the tongue condition was noticed a few weeks later. The patient considers that both conditions have gradually become worse. No previous illness and no family history of importance.

Physical examination.—The pupils, fundi and ocular motor nerves are normal. The tongue shows hemiatrophy with fibrillary tremor. Right middle-ear deafness. Other cranial nerves normal. Sensation normal. Slight general weakness and wasting of left arm; shoulder-girdle muscles normal. Left thenar, hypothenar, first and fourth interosseous muscles appear weak and slightly wasted. Arm-jerks and abdominal reflexes normal. Knee-jerks, very sluggish, even on reinforcement. Ankle-jerks: right brisk, left sluggish. Plantars flexor.

No apparent weakness nor wasting of his legs. Co-ordination normal.

Blood: Wassermann reaction, negative. Cerebro-spinal fluid: cells and protein, normal; Wassermann reaction, negative.

Giant-celled Glioma (Giant-celled Spongioblastoma Multiforme).

By Dr. W. E. CARNEGIE DICKSON.

H. B., male, aged 37. Admitted to West End Hospital for Nervous Diseases, June 10, 1926.

History.—Syphilis in 1916 whilst in the Army. Treated with ten injections of "606." No other treatment. Had suffered from headaches since he left the Army in 1919, these becoming more severe during the last twelve months, and affecting top and back of head. Insomnia and attacks of diplopia for four weeks. Headaches became more localized to frontal region five weeks before admission, and for seven weeks a daily attack of vertigo. During these seven weeks three attacks of vomiting.

On admission.—Pupils equal, circular, central, and reacted to light and accommodation. Papillœdema in both eyes. Slight lateral nystagmus.

Sensation, reflexes, co-ordination and sphincters normal. Wassermann reaction negative in both blood and cerebro-spinal fluid.

On June 18, a right subtemporal decompression was performed by Mr. Bathe Rawling. The eye condition recovered completely in three weeks, but mental symptoms developed.

On August 9, septic broncho-pneumonia supervened, with pulsus alternans, and three days later the patient died.

Post-mortem.—Permission was granted for the examination of the brain only. On cutting this across horizontally at the level of the upper parts of the lateral ventricles, a very large, soft, tumour-like mass was found destroying the greater part of the frontal regions, the left frontal pole being rather more affected than the right, the condition having evidently started in the former, and later invaded and compressed the latter. The mass was partially necrotic, and showed extensive hæmorrhage into its substance, some of the surviving more peripheral parts being of a pale brownish to slightly pinkish-brown colour.

Microscopically.—The appearances were very characteristic and striking, and were those of a "mixed-celled" glioma, with the development of enormous numbers of neuroglial giant-cells of all sizes, containing from two or three, up to a couple of dozen or more, rounded or slightly oval, vesicular nuclei—some of the cell-bodies measuring 100, or even 120, microns in diameter. The nuclei of many of these giant-cells were arranged peripherally, very much resembling those in tubercle or syphilis, but others were in "mulberry masses," whilst others again were scattered diffusely throughout the cytoplasm. Between these giant-cells there are numerous smaller tumour-cells—rounded, irregular, or in some areas somewhat spindle-shaped. In some parts, thin-walled vascular sinuses or dilated capillary blood-spaces were numerous; and, in some of these thrombosis has taken place, often with an excess of polymorphs in, and also slightly around, them. Numerous hæmorrhages have also occurred from these thin-walled blood-spaces; and in some parts of the tumour there is extensive necrosis.

Oligodendroglioma of Floor of Third Ventricle.

By Dr. W. E. Carnegie Dickson.

J. P., male, aged 6. Admitted to West End Hospital for Nervous Diseases, April 12, 1926.

History.—The patient was a first child; chloroform and instrumental delivery. Diagnosed as suffering from primary optic atrophy of both eyes at 5 months of age. Complained of slight pain in left leg about Christmas, 1925. In second week of January, 1926, sudden attack of headache, vertigo, and vomiting. Unable to walk since this attack. He had marked trembling of hands and knees; condition became progressively worse, with frequent attacks of vomiting, and distinct change in character, the boy becoming perverse and difficult to manage.

On admission.—Pupils dilated, equal, central and circular. Did not react to light. Right eye completely blind; with left eye can count fingers. Tendency to convergent strabismus; weakness of both external recti; eyes could move only just beyond mid-vertical line, and could not be elevated above mid-horizontal line. No nystagmus or ptosis. Secondary optic atrophy of both eyes. Anosmia. Weakness of movement of left side of face, with partial obliteration of the naso-labial fold. Loss of sense of taste. Rapid pulse, 125. Screamed

when washed or moved in any way. Spastic paraplegia. Unable to feed himself, and had incontinence of urine and fæces.

On May 6 bilateral subtemporal decompression was performed by Mr. Bathe Rawling. Patient died on the seventh day after operation.

Post-mortem.—On reflecting the scalp the skull was very thin, and both anterior and posterior fontanelles were still slightly, but distinctly, membranous.

The cerebral membranes showed nothing of special note, except for some hæmorrhagic infiltration in the neighbourhood of both operation-wounds. The convolutions were extremely flattened and pale, but there was no naked-eye evidence of any meningitis.

On raising up the brain from the base, a projecting soft tumour-like mass was found in the interpeduncular space, extending from the upper margin of the pons to well in front of the optic chiasma, the latter, along with the tuber cinereum and infundibulum being involved and obscured by the mass, which extended on each side to the tips of the temporo-sphenoidal lobes. Corresponding to this projecting mass at the base of the third ventricle, the pituitary fossa was pressed upon, being wider and shallower than normal, the gland itself being compressed against the bottom of the fossa, so as to become distinctly saucer-shaped and widened. In the position of the tuberculum sellæ of the sphenoid there was another rather shallower depression, giving an appearance of doubling of the sella turcica—this anterior depression being due to the pressure of the tumour in the region of the optic chiasma. The proximal or posterior halves of the intracranial portions of the optic nerves were both also involved in the tumour; the left being narrowed and degenerated in appearance; the right nerve being some three or four times as bulky, soft, and œdematous, and perhaps invaded by new growth.

The third nerves did not appear to be specially compressed or involved in the tumour; but the sixth nerves were distinctly compressed against the bone.

There was distinct excess of cerebro-spinal fluid within the brain, and, after fixation, horizontal section showed a very marked degree of chronic hydrocephalus, involving both the lateral and the third ventricles. There was embedded in the floor of the latter a soft, rounded, pinkish-brown tumour, about the size of a small cherry, more or less in the middle line, but projecting rather more to the right than to the left side. The feel and appearance of this were rather suggestive of a "cystic" tumour, but, on cutting into it from above, it was found to have a soft peripheral part, with a necrotic and hæmorrhagic-looking interior.

Microscopically.—Sections from both the under and upper aspects of the tumour showed an identical structure, viz., that of an oligodendroglioma, composed of small cells with dense spherical nuclei, surrounded by rather indefinite feebly-staining cytoplasm, between which there was what Bailey and Cushing describe as "indefinite material which stains neither for neurofibrillæ, neuroglia, nor for connective tissue," and they add that "this material may give the growth somewhat the appearance of the cross-section of a plant." Some of the small blood-vessels surrounded by tumour-cells show

an "irritative" proliferation of their endothelial cells, sufficient in some instances to fill their lumen and form little solid buds or masses. Both optic nerves show great thickening of their fibrous-tissue sheath and framework, with, in the left, advanced, and in the right, complete, atrophy and disappearance of the nerve-fibres; though in the portions examined from the nerves as they emerged from the tumour there was no actual infiltration of them by the tumour-cells.

Progressive Muscular Atrophy of Syphilitic Origin.

By Dr. LEWIS YEALLAND.

E. G., male, aged 50. Occupation—postman, formerly Regular soldier.

History.—Enteric fever, 1896; syphilis, 1901, treated by "mixture" for two months; no modern therapy. Gun-shot wound, 1918, and lost right eye. In December, 1922, a progressive wasting of muscles of both hand and arms commenced, more marked on the right side, and of the posterior cervical muscles. Weakness of muscular power in these areas became definitely noticeable two years later.

Examination.—Head-drop due to weakness of posterior cervical muscles, with consequent lordosis and slight cervical scoliosis. Wasting of muscles of pectoral girdle and winging of scapulæ, right greater than left. Muscular weakness and wasting is marked in the right hand and arm, but is mainly limited to the hand on the left side. All intercostal, pectoral, and abdominal muscles react to faradism, but excitability subnormal. Deep reflexes of right arm diminished. Right knee-jerks diminished. Ankle-jerks absent on both sides. Plantars flexor. Blood-pressure: systolic 160; diastolic 95.

Pathological reports.—Blood: Wassermann reaction positive. Cerebro-spinal fluid: Wassermann reaction strongly positive. Total protein 0·08 per cent. Globulin in marked excess; cells, mostly lymphocytes, in excess.

Huntington's Chorea.

By Dr. LEWIS YEALLAND.

W. N., aged 59.

History.—Pneumonia in 1890; chronic bronchitis since 1918. In September, 1925, unsteadiness of gait and involuntary twitchings of ankles commenced, progressed, and involved the shoulders and arms; more marked on right side.

Family history.—Father suffered from gout; mother had some "jerky complaint"; one sister has Huntington's chorea, the other is alive and well; two brothers are alive and well.

Examination.—Suffers from gout; bronchitis; extremities cyanosed; losing weight; speech—slow, slurring, with syllable stumbling; slight facial asymmetry; gait ataxic; choreic movements; mentality failing; inco-ordination of movements of arms not marked.

Pathological report.—Blood Wassermann reaction negative.

CRITICAL REVIEW.

Aphasia and Kindred Disorders of Speech. By HENRY HEAD. 2 vols. Pp. 979. Cambridge: The University Press. 1926. Price 63s.

The significance of Head's experimental study of *Aphasia and Kindred Disorders of Speech* cannot be fully understood if the latter is considered apart from the rest of his work. Together with the whole of his earlier investigations into the results of various disturbances of afferent sensibility, his present researches issue in a general view of the ways in which life and mind have developed and are organized. This general view is expounded and discussed very concisely in the four final chapters of Part I of the book now under review.

The two master processes, alike of organic and of mental development, are integration and adaptation. Now the key to an understanding of these processes is the fact that no reaction of a living organism, however simple and immediate it may appear to be, can be satisfactorily studied in isolation. This statement seems both obvious and clear. Yet its implications, Head maintains with perfect justice, as it appears to me, are revolutionary in so far as the study of aphasia is concerned. The bulk of past work on aphasia has had a definite anatomical bias. To this nobody need raise any objection. However the subject is approached, language defects may be shown to involve very important anatomical lesions or abnormalities. These structural defects may, moreover, be shown to differ as the specific language irregularities, or groups of specific irregularities, differ. But the traditional method of treatment has gone much further than this. It has assumed that a specific language defect or group of defects can be properly studied for itself, in itself, and by itself. It has thus issued naturally in the doctrine of relatively narrowly defined anatomical areas within which certain equally narrowly defined mental, or psychological, processes are regarded as taking place. Its question is: "Given a definite psychological process, where in the central nervous system must we regard this as happening?" Head desires to change the whole direction and leaning of the problem. "Granting a certain anatomical lesion," he says, "the first question we must raise is, what precisely are its effects?" The moment we investigate this problem we find that the activity of any "centre" in the central nervous system is inevitably bound up with that of innumerable other parts, cortical and subcortical, which have all been brought together in the course of development, and which somehow have to be regarded as functioning together in normal daily behaviour. More than this, the part played by any element in the complex network or pattern of activities which any response of the central nervous system brings into play, cannot be accurately determined by cutting it out of that pattern. For when, by anatomical lesion or in another

way, the possibility of a specific element of response is removed, the whole pattern has to undergo reorganization. Thus the new response is not the old one simply minus one of its elements. It is genuinely a novel response.

If we turn our attention from a study of the structure which is in some way at the basis of conduct to that of the activities of conduct themselves, we find that exactly the same things are true. Head's earlier work showed that not even the apparently simple discrimination of sensory modes and qualities, the apparently direct appreciation of sensory differences of size, shape, texture, posture and the like, can be understood apart from the complex setting in which they occur. With "high level" activities such as the use of language this almost infinite complexity is more obvious still. Looking at the use of language when it is perfectly acquired we can readily see that much must have gone to its making. There are, for example, the direct interpretation of immediately presented sensory situations, the direct matching or comparison of situations presented through different senses; the development of substitute modes of reference—images, for instance—whereby situations no longer immediately presented to sense can be made use of; the acquirement of a way of dealing specifically with the important relational factors of external situations, and no doubt many other processes also. But we cannot take any one of these, study it by itself and then conclude that we have found exactly how it operates in the complex activity called using language. Further, since some of these processes can perfectly well be carried out without the use of language, it is highly probable that language disturbances may affect other than specifically language activities.

Another way of putting all this is to say that whenever any stimulus, or group of stimuli, bring about organic response, the organism has to be regarded as mobilizing the whole of its available resources for dealing with the situation presented. Stimuli have reactive value or significance, that is, never merely for a local part of the organism, but for the organism itself. And this is precisely what is meant when it is said that adaptation is a characteristic of all organic reactions. There is no response dealt with in physiology or in psychology which is not built up by the historical combination of numerous simpler reactions. Also there is no response dealt with in physiology or in psychology the simpler constituents of which can be unequivocally discovered by analysis of the more complex reaction once it has been acquired. There are historical elements, but these are not found by analysis.

Such considerations are vitally important if Head's technique for the study of aphasia is to be understood or intelligently criticized. He devised and applied a number of specific tests and watched the performances of his patients under the test conditions. The tests themselves range from problems of simple sensory "matching" or identification, in which some common object which has been seen is presented tactually and thus identified, to problems the solution of which involves definite formulation in language terms. Moreover, those involving language formulation range from simple naming tests to tests depending for their solution upon a capacity to respond in such a way to

the manner in which concrete details of a given situation are related together that the identical relationships may be utilized in a new setting. To urge that some of these tests are not specifically language tests is misplaced criticism. For the objection depends on the theory that a language response is nothing but a language response, whereas in reality it is based upon and bound up with numerous other integrated and adapted responses without which it could never have been acquired, and which contribute to its functioning when it is acquired.

For another reason the tests mark a great advance. The acquisition of language and the loss of language have many features in common. If Head is right the general effect of a specific language disturbance is to throw the patient back upon earlier acquired and relatively less complex modes of dealing with the problems that face him. He does not literally regress to an outgrown mode of response, because in some respects his adult activities are undisturbed, but he does tend to rely upon more childish integrations. Thus both the formation and the use of mental images, which are instruments of adjustment of a simpler and more concrete order than words, may be not merely undisturbed but actually facilitated—a point entirely obscured in much of the earlier work. Or again, situations which call forth reactions arranged in a fixed serial order are effectively dealt with; those which demand constant rearrangement of reactions in accord with varying relational factors produce complete breakdown. Now a great deal of the value of Head's technique is that it enables us to use the same precise methods for the examination of language functions during the process of their acquisition as for their failures under the disorganizing influence of aphasia. For the first time the possibility of very important exact comparative work is clearly opened up.

As is now well known, Head proposes a new classification of aphasic defects. This will, no doubt, be severely attacked on various different grounds. It will be said that the "verbal," the "nominal," the "syntactic," and the "semantic" types greatly overlap. Assuredly they do. Head is emphatic about this himself. So do all other biological types or classes.

It will be urged that here is nothing new after all. For the "verbal" and "syntactic" types are defects in the *use* of language forms—words and propositions; while the "nominal" and "semantic" types are defects in the *understanding* of language forms—words and propositions. That is broadly true, but nevertheless the proposed classification does directly raise some important problems Two of these are: the significance and justification of thus differentiating word defects and proposition defects, and the possibility of treating all these defects, as Head does, as various ways in which symbolic formulation break down.

Again it will be said that many of Head's illustrations, particularly of the "syntactic" and "semantic" types, are exactly like the "scattered speech" reactions which may sometimes characterize certain psychotic and psychoneurotic states. The implication appears to be that these ought not to be regarded as belonging to the specific aphasic class of phenomena. Recognition

of the great complexity and range of language integrations, however, robs this criticism of much force.

The proposed classification is in fact meant to be used as a tool, and in no other way, for clearing a path through an apparent jungle of facts. If a more efficient tool can be found, well and good. But in the meantime this classification is constructed upon a principle which leads directly to Head's important discussion of the nature and functions of thinking and their relation to the use of language. Thinking in general possesses three outstanding characteristics: (*a*) It is a capacity for dealing with situations at a distance, and hence involves the *use* of symbols; (*b*) it is a capacity for responding to the qualitative and relational factors of a situation in their *general* aspect, and hence involves the *formulation* of symbols; (*c*) in the great majority of cases it is a capacity for retaining the concreteness of a given situation, and at the same time for utilizing these abstract and general qualitative and relational features. We can watch this very complex capacity growing up.

First, the organism responds only to immediately presented external stimuli. But there is no observable case in which the conditioning of the response can be stated in terms of a narrowly isolable stimulus. The response depends upon an arrangement of preceding responses which have been already organized. The name given to these organized responses, which may produce their effects in the entire absence of any awareness of them on the part of the reagent, is *schema*. At any level of physiological response a number of these *schemata* must be assumed to be in operation.

Now the simplest order of arrangement of the effects of these sensory responses into *schemata* is the direct sequential or serial order. Every sensory response contributes to a determination of the next succeeding response of the same mode. But more than this, a response in one mode, say visual, can be directly equated with a response in a different mode, say tactual. This is what Head calls "matching." It is a process which I suspect to be of greater complexity than he indicates, the limits of accuracy of which demand a far more careful study than he attempts. In "matching" symbols first begin to be used; one sensory pattern stands for or symbolizes another. Such sensory symbols, however, involve a very complete repetition of the details of the original presentation for which they stand, and cannot operate if there is much of a time gap between them and their original. A step forward is taken by the development of "images." To use mental images, according to Head's treatment, is to develop a device for picking certain concrete items out of the settings in which they originally occurred, and for utilizing them irrespective of the precise sequential order to which they actually belonged in the first place. I am, for example, faced by some practical difficulty which demands a response modelled upon something that happened to me six months ago. I thereupon directly reinstate this six months' old happening in visual, auditory, or other terms. To do this I pick it out of the exact series in which it occurred, but at the same time retain its essentially concrete character. Thus it helps me over my immediate practical difficulty. Such relatively high-level

imaging is to be distinguished sharply from relatively low-level "repetitive memory," when, if breakdown occurs, a series of reactions must be begun over again from the beginning and carried out in fixed serial order if the difficulty is to be overcome. This case is, for example, constantly illustrated by the child reciter.

Both "matching" and imaging involve the first of the three characteristics of thinking, though not to any great degree the other two. The image method is always trying to find some way of dealing with the general aspects of presented situations, but never achieves much success. Words, and words only, seem to be equally adapted to both concrete and general and relational features. We have names for the first, prepositions, conjunctions, and various phrase forms for the second. Language defects, then, are defects of symbolic *formulation*, but as this has grown out of and been made possible by the simpler and earlier use of sensory and imaginal symbols, the latter may also be specifically affected as a result of derangements of speech.

A study of the principles according to which these related activities are affected leads us to Head's notion of "vigilance." An organism must be regarded as possessing a number of responses ready to come into operation to meet demands set up by any incoming new stimulus. Many of these responses, and their effects, are organized into the *schemata* already mentioned. In any given case what response is evoked depends partially on the nature of the stimulus in relation to the *schemata*, and partially on a general vital state of the central nervous system by virtue of which the latter can exercise a more or a less complete selective control. This vital state and its correlated functions of selective control Head calls "vigilance." Whether a stimulus or situation "produces" a series of relatively simple reflexes, or a very highly complex and organized response, never depends merely on the stimulus or situation itself. It depends upon the relation of the stimulus or situation to those modes of reaction which the subject has already organized and available for use, that is, upon the *schemata*. And which of these come into operation depends directly upon the activity termed "vigilance." If the latter is active to a high degree, then the most complex, lately acquired and highly integrated *schemata* have functional control over the less complex, earlier and less highly integrated types of organic response. But if vigilance is lowered, as it may be by structural injury, by disease, by drug intoxication, by fatigue, and by sleep, the more highly integrated responses are thrown out of action and historically simple forms reappear. Again it must be stated, however, that they never reappear exactly, but in a form which is specific to the general development and state of the organism at the time. A stimulus or a situation is presented. The temporary state of vigilance allows certain organized modes of response to function, and these control all the less highly organized ways of dealing with the same type of situation. It does not matter whether the *schemata* which come into play are those highly complicated reactions called "conscious" and dealt with by the psychologist, or the relatively less complex and earlier reactions frequently termed reflex and dealt with by the physiologist. Their

mode of controlling simpler responses is always the same, and "vigilance" is a factor the general character and functions of which persist throughout the whole history of organic and mental life.

Such, in brief, is the theory which Head presents persuasively and clearly, and illustrates constantly in *Aphasia and Kindred Disorders of Speech*.

Whatever may be the ultimate verdict upon this theory, everybody must admit that Head has carried through a constructive effort of first-rate importance. But the theory must be subjected to most rigorous criticism. The basic notion of "vigilance" itself raises exceedingly grave problems. It may be due to a certain psychological bias on my part, but I cannot escape from a suspicion that "vigilance" is only another name for what appears in many general theoretical psychological systems as "attention." On the face of it, it may appear that the former has none of the *conscious* affiliations of the latter. But this is not a point of any importance, for the notion of "attention" as a controlling factor operative only at the conscious level of response is one which is always breaking down. Both alike seem simply to be names for the fact that under certain specific conditions certain types of organized response will appear and will be in control of behaviour. If vigilance is taken to be this, it appears to me that it does not itself explain anything whatsoever. It merely helps us to formulate problems the whole burden of the explanation of which has got to be laid upon a study of the characteristics of the *schemata* which, in given instances, come into operation. If we try to push "vigilance" further than this, still keeping it definitely distinct from the *schemata* whose expression it is supposed to allow, it is extraordinarily difficult to avoid the notion that "vigilance" is a factor which underlies all organic response, varying quantitatively only, and more or less active according to the amount of nervous or mental "energy" which is at the disposal of the organism at any given moment. It is perhaps not uninteresting that the conception of "vigilance" was first publicly developed in connection with a discussion of nervous and mental energy. I am, however, almost certain that Head would warmly repudiate this sort of quantitative interpretation of "vigilance." And for my part I am quite convinced that the notion of "energy" in this sense, common as it nowadays is, is one with which both physiologist and psychologist had much better have nothing whatever to do.

I may, however, have misunderstood some very vital part of the argument. For to Head vigilance appears to be a potent explanatory principle. He holds, for example, that it explains—by putting out of court—the whole intractable mind-body problem. Since "vigilance" is a factor operating alike at the highest levels of conscious adaptation and at the lowliest levels of reflex activity there is no special mind-body difficulty. It is, he asserts, as easy to understand how conscious activities control the higher reflexes as it is to understand how the higher reflexes control the lower reflexes. Obviously this statement could be put another way. We might say: "It is just as difficult to understand how the higher reflexes control the lower reflexes as to understand how conscious activities control the higher reflexes." The second state-

ment is as unexceptional as the first, although its emphasis is different. The presence of vigilance throughout the whole line of growth may mean not that the body-mind type of problem is solved, but that it is ubiquitous.

The trouble is, in fact, that as soon as ever we try to give "vigilance" any positive characteristics—and we can hardly escape doing this—we come at once upon the *schemata*. It is indeed upon the development, interrelations and manifold activities of the *schemata* that the burden of explanation, in any set of proposals such as this, will have eventually to lie. So far as general theory goes, I believe that it is in his treatment of *schemata* that Head has achieved the most original and most profoundly important results. Yet here again there is a vast amount yet to be done. Building the *schema* is an active process; linking new incoming stimuli with their appropriate *schemata* is an active process; interrelating the various *schemata* is an active process; the control of the *schemata* over less highly integrated organizations is an active process. Precisely how are all these active processes to be differentiated from one another? Precisely how do they work? And again the *schema* is an arrangement of responses; it is also, regarded from another point of view, an arrangement of material, sensory at a lowly level, affective at a perhaps slightly higher level, imaginal at a higher level yet, and eventually ideational and conceptual. But its functions as arrangement of responses are not to be confused with its character and functions as arrangement of material. Towards the solution of many of the problems raised Head makes many illuminating and brilliant suggestions. He would, I am sure, be the first to agree that much yet remains to be discovered.

The whole discussion is stimulating and attractive to the last degree. It goes without saying that it would be neither were it not highly provocative of criticism and also a long way short of complete finality.

F. C. BARTLETT.

Notices of Recent Publications.

Leitfaden der neurologischen Diagnostik. Von Kurt Singer. 2te Auflage. S. 246 mit 34 Abbildungen. Berlin und Wien; Urban und Schwarzenberg. Price 9 M.

In this book symptoms and physical signs are dealt with rather than diseases or clinical entities. Thus one chapter is devoted to palsies of different nature, another to disturbances of sensation, others to muscular wasting, changes in the reflexes, involuntary movements, tremor, convulsions, neuralgia, headache, &c. The author's aim has been to provide the student and general practitioner with a short guide by which they may learn to recognize the nature and the possible origin of the symptoms they observe, and thus come to a diagnosis of the morbid condition affecting the patient.

Within this scope the book will certainly be useful, though there are many points in it on which adverse criticism can touch. Some of the more important signs and symptoms are described so inadequately, despite the considerable size of the book, that no one untrained in modern neurology could profit by a perusal of these pages. From the short paragraph on the disturbances of sensation by cortical lesions, for instance, it would be impossible to gather an idea of what should be sought in the examination of the patient, or, on the other hand, deduce from an examination the site of the lesion.

Again, the few pages on disturbances of vision and defects in the visual fields are entirely inadequate, and from the description given here alone few could determine which ocular muscle is at fault in a case of diplopia. A more careful description of the modes of examination of a neurological patient, and of the tests which the student and general practitioner should employ, would have been welcome. A more liberal supply of illustrations and especially of diagrams would have increased the value of this book; they could profitably replace some of the diffuse and redundant text.

Neurologie. Par A. Tournay. Pp. 312. Paris: G. Doin. 1926. Price 19.20 francs.

This small volume consists of short compressed paragraphs, such as a lecturer might use, on the clinical features and the treatment of the more important nervous diseases, rather than a detailed account of them. Despite its small size it is remarkably complete, and, as far as one can judge from a casual perusal, accurate in statement and judicious in advice, especially in the sections on treatment which are a prominent and useful feature. It should be consequently useful to the student whose time or opportunity for more systematic study is limited.

Heart and Brain: Lectures on Physiology. By GIULIO FANO. Translated by Helen Ingleby. Pp. 142. London: Oxford University Press. 1926. Price 8s. 6d.

The six lectures included in this volume were recently delivered in Spanish Universities. The title of the book is due to the fact that in these lectures the author deals mainly with certain functions of the brain and heart, since he believes they lend themselves to general application. It has not been his aim to present the sum of knowledge attained by recent investigations in the subjects which he treats, but rather to advance certain general conclusions on the nature and mode of action of the living body or of some of its parts; it is in fact largely on his own work that he relies, but this gives his presentation a peculiar personal, or, as he claims, an autobigraphical character that adds to its interest and charm. The reader will find here not so much an accumulation of observations or discussion of hypotheses, as the outlook of an ageing scientist on the fruits already harvested, and the future prospect of the subjects to which he has devoted a large part of his life. To younger workers some of his conclusions may appear unwarranted and perhaps even depressing, as his rejection of the theory of evolution; his assumption of a cosmic will which moulds living things, using some of the first made forms to create new ones; and his insistence on the teleological significance of the phenomena of life; but as to many others who in their day have contributed largely to our knowledge, the immensity of our ignorance is more apparent than the little we have learned.

The first two chapters deal with so-called living matter, the next two with relations between inhibition and will, and the last two with excitability and automatism—all will prove interesting and instructive to the ordinary layman as well as to the physician who is not primarily a physiologist. The translation of the book into English has been excellently carried out.

Theoretical Biology. By J. von UEXKULL. London: Kegan Paul, Trench, Trübner and Co. 1926. Pp. 362. Price 18s. net.

It seems strange, at first sight, that one who, as a zoologist, is a protagonist in the mechanistic School to which Loeb, Bethe and Nuel belong, should have soared in this book into philosophical heights to which it is difficult to follow. He seems to be an example of the not very rare psychological type to which the spiritualistic physicist belongs. The work is said to be "a serious attempt to extend the doctrines of Kant's philosophy into the realm of biological thought." It has much of Kant's obscurity—partly due perhaps to unsurmounted difficulties of translation. Its contents seem to enforce the moral, *Ne sutor ultra crepidam.*

Ventrikulographie und Myelographie in der Diagnostik des Zentralnervensystems. Von O. JÜNGLING und H. PEIPER. S. 195, mit 210 Abbildungen. Leipzig: G. Thieme. 1926. Price 16 M.

This monograph is part of a system of medical radiology which is now appearing; it is procurable separately. Its first part, written by Jüngling, deals with ventriculography as introduced by Dandy. The technique for the introduction of air into the ventricles by ventricular, lumbar and suboccipital puncture is carefully described, as well as the best methods of radiographic examination. After a short description of the normal appearances when either the ventricles or the subarachnoid space is filled with gas, the author goes on to discuss the interpretation of the abnormalities which the method may reveal in X-ray plates, its use in the diagnosis of hydrocephalus, cerebral tumour and other intracranial lesions, the contra-indications for its employment, and the symptoms the introduction of air may produce.

In the second section Peiper deals similarily with the technique, the interpretation and the value of the injection of opaque substances, generally colloidal iodine in oil, in the diagnosis and the localization of vertebral and spinal lesions. Both sections are copiously illustrated by excellently reproduced drawings and radiographs, which will be of great service to the inexperienced who wish to interpret the changes shown on their own plates.

Klinische und Liquordiagnostik der Rückenmarkstumoren. KARL GROSZ. S. 127. Wien: J. Springer. 1925. 6.90 M.

This useful and instructive monograph is based mainly on the author's extensive personal experience of tumours which either invaded or compressed the spinal cord. He publishes the clinical accounts and the verifications of the diagnosis by either operation or autopsy of many of his cases, which he divides into the ordinary types, vertebral, extradural, intradural and intramedullary, and the special features of each group are discussed. The individual symptoms, and their significance and value in diagnosis and localization, are dealt with in the second part of the book. Here the changes in the cerebrospinal fluid, their significance in diagnosis, and the use of lipiodol are also considered.

Les différentes Formes de l'Arsénicisme. Par KARL PETRÉN. Pp. 128. Paris: Masson et Cie. 1926.

As a result of an epidemic of arsenical poisoning in Sweden some years ago, a Government Commission was appointed to investigate the circumstances of its origin and the different manifestations which the intoxication may produce. Professor Petrén was President of the Commission, and here publishes in great detail the results and conclusions to which it came. Special attention is given to the poisoning by household fittings, as wallpaper, clothes, stuffed birds, &c., as well as to other sources, and to the different forms and modes in which arsenic may enter the body.

The symptoms of both acute and chronic poisoning are fully described, including arsenical polyneuritis, which was not however a common symptom. A special feature of the report is the employment of micro-analytic tests for the presence of arsenic in the blood and secretions.

Cavernous Sinus Thrombophlebitis, and Allied Septic and Traumatic Lesions of the Basal Venous Sinuses. By W. P. EAGLETON. New York: The MacMillan Co. 1926. Pp. 196.

This book consists mainly of a study of twenty-five personally observed cases of thrombosis of the cavernous sinus, but reference is also made to thrombosis of other dural sinuses and to cases of arterio-venous aneurysm of the cavernous sinus. According to the author septic infection of the sinuses is always due to an infected thrombus extending backwards from an infected area, generally the mastoid or nasal sinuses, and not to a direct extension of the suppuration.

Thrombosis of the cavernous sinus is divided into six groups according to the route by which the infection arrived, and the chief clinical and pathological features of each of these is described, and their diagnosis carefully considered. The chapter on operative treatment reveals the ingenuity and courage of the author, but even in his hands the mortality remains very high. He makes the interesting suggestion to give the sinus "rest" by ligature of the internal carotid artery.

A French edition of the book, published by Masson et Cie, Paris, has appeared at the same time.

Les Troubles mentaux dans les Tumeurs cérébrales. Par H. BARUK. Pp. 396. Paris: G. Doin et Cie. 1926. Price 48 fr.

The author studied thirty cases of cerebral tumour, particularly with reference to the mental disturbances that appeared during the course of the illness, and selected other cases from Souques' records, making in all fifty-five cases, thirty-five of which were verified anatomically. In forty-one patients there were mental symptoms, and in fifteen pronounced psychical abnormalities. The general features of the mental troubles are first studied, and an attempt is then made to correlate them with the localization of the lesion in the brain; as was to be expected, they were most commonly pronounced when the tumours invaded the frontal lobes and the corpus callosum, but the author rightly emphasizes intracranial pressure and cerebral œdema as important causal factors. Many of the cases are reported in full, and these, with the author's conclusions, will make the book interesting and instructive to both the neurologist and the psychiatrist.

La Syphilis nerveuse. Par A. SÉZARY. Pp. 208. Paris: Masson et Cie. 1926. Price 3s. 6d.

This small monograph has been written by a syphilologist and bears the mark of his slight acquaintance with the clinical forms of nervous syphilis. The following paragraph gives a fair indication of his attitude: "Selon la tendance habituelle de la médecine contemporaine qui, en présence d'une affection chronique de cause indéterminée, envisage toujours la possibilité de son origine syphilitique, on s'est demandé si la sclérose en plaques n'était pas due au tréponème pâle." However, after a long discussion he comes to the conclusion that, as a rule, syphilis plays no part in the etiology of disseminated sclerosis.

The book contains nothing new or noteworthy. Arsenical compounds and bismuth are preferred to mercury in the treatment of nervous syphilis; his only rule seems to be injection after injection till some change is found in the cerebro-spinal fluid.

Medizinische Psychologie. Von E. KRETSCHMER. 3te Auflage. S. 273, mit 24 Abbildungen. Leipzig: G. Thieme. 1926. Price 15.30 M.

The appearances of the previous editions of "Kretschmer's Medical Psychology" have been already noticed in this Journal: both of these were small handbooks intended chiefly for the student, and in many parts so compressed that they were not easy reading. The third edition has been much expanded and appears in a different and more readable form. Its new pages are due mainly to a fuller discussion of the many questions presented by recent physiological investigations, and a greater attention to the results of experimental psychology. The methods of psychological examination are also described in more detail.

This tendency of the author to base his psychological hypotheses more intimately on experimentally verifiable facts is particularly welcome; these new or expanded sections also make it possible to follow the author more easily in the development of his subject matter. It is surprising, however, that more attention has not been given to Pavlov's work on the cerebral conditioned reflexes, for in the future these will certainly demand more notice in psychological theorization. The chapters on temperament and personality are among the most valuable and interesting in the book.

This, the third edition, can be recommended to both student and practitioner, even more strongly than the earlier editions which it displaces.

The Sheffield Outbreak of Epidemic Encephalitis in 1924*: Report of a Sub-Committee of the British Medical Association.* Pp. 73. London: His Majesty's Stationery Office. 1926. Price 1s. 9d.

This report, published by the Medical Research Council, deals with an outbreak of epidemic encephalitis in Sheffield, where 301 cases were notified in 1924. The special value of the report is that all of these cases have been

followed for at least twelve months from the onset. Professor Wynne writes on the epidemiology of the epidemic, but is unable to deduce from its study any new conclusions. Professor Douglas's attempt to transmit the disease to smaller animals failed and his pathological investigations gave no new results. The study of the clinical aspects of the disease and of its earlier sequels by Professor Hall and Dr. Yates is particularly important, as they had the opportunity of observing a sufficiently large number of cases under more or less uniform conditions to allow them to make a statistical record of the separate symptoms and their prognostic significance.

Neurologische Wandtafeln : zum Gebrauch im klinischen, anatomischen und physiologischen Unterricht. Herausgegeben von F. Müller und H. Spatz. München : J. F. Lehmann. 1926. Price 108 M.

In clinical instruction, not less than in the teaching of the anatomy of the nervous system, adequate illustrations in the form of nature-like reproductions of the brain and of stained and unstained sections of its parts, as well as diagrams of the connections of these parts, are essential. Such illustrations abound in textbooks of anatomy and neurology, but hitherto the teacher of classes of students has had to rely largely on his own diagrams, the making of which consumes time, or on lantern slides which offer to the student as a rule only a momentary glance of a complicated picture. Some years ago Strümpell and Jacob issued a set of large charts which could be hung up in the lecture-room, but these are no longer procurable, and those who are lucky enough to possess them are sadly conscious that though still useful they are out of date in many respects.

The series of charts or wall-tables now issued by Müller and Spatz are described as a new edition of those published by Strümpell, but most of them have been modified to correspond to our more detailed knowledge of the anatomy of the brain, and their number has been increased to eleven. Nine of the charts measure $3\frac{1}{2}$ by $4\frac{1}{2}$ ft.; the other two, which contain diagrammatic representations of the more important fibre tracts through different levels of the nervous system, are 4 ft. 6 in. by 7 ft.

The first six charts are remarkably true representations of the macroscopic appearances of the surface of the brain and of sections through it in both the horizontal and frontal planes. Two sections are reproduced on each chart on such a scale that all the important features visible to the naked eye in the normal brain can be easily seen by the student in the largest lecture hall. In the next three charts transverse sections of the brain-stem and spinal cord as seen when stained by Weigert's method, are shown in colour. There are sections of twelve different levels of the brain-stem and in the chart of the spinal cord there are, in addition to sections of six different levels, coloured diagrams showing the position of the more important tracts in these sections, and a diagram of the connections of the sympathetic system. In the two

largest charts several cross sections of the brain-stem and cerebellum are shown in outline, with the more important structures of them represented diagrammatically in various colours.

The main illustrations are not disfigured by legends, but beside each there is a small diagram in which all the more important structures are named; this will make them particularly useful to the student who desires to study the charts alone. A small book containing a description of the figures, each of which is reproduced on a small scale in black and white and adequately legended, will help both the teacher and the student.

These charts are essential to the equipment of every neurological clinic, and of every anatomical department where teaching by lectures and demonstrations is undertaken.

Die Stammganglien und die extrapyramidal motorischen Syndrome. By F. LOTMAR. Pp. 135. Berlin: Julius Springer. 1926.

Within the compass of a monograph of 135 pages the author has attempted to summarize our knowledge of the morbid anatomy of diseases involving the corpus striatum, the symptomatology of these lesions, and the various speculations as to the functions of this mass of grey matter which have been built upon this clinico-pathological foundation. There could be no more striking illustration of the vast literature which has grown up round this region of the brain within the past fifteen years, or of the intensive study to which it has been subjected in this period, than this tightly packed and condensed statement with its bibliography of 500 names.

The author has not attempted any evaluation or critical analysis of the various recorded observations, clinical, pathological, or experimental, nor of the hypotheses based thereupon. All statements of fact and all conclusions go down in his pages as of equal value, and the reader is left to choose for himself which among the welter of conflicting observations and mutually incompatible speculations he will adopt for his own. There is, however, at the end of each section a brief and lucid summary of the evidence presented therein.

It is clear, therefore, that a monograph of the kind, while it does not throw any fresh light upon the difficult problems with which it deals, and while it is incapable of summary, yet will be of very real value to all who are working upon the subject, and will prove a useful work of reference for those who wish to ascertain the facts of observation so far on record upon any particular aspect of the symptomatology and pathology of the corpus striatum. It appears, however, that a critical analysis of this information in terms of the normal functions of the corpus striatum has yet to be written. Lotmar's monograph is excellent raw material for such an analysis.

Aphasia. By S. A. KINNIER WILSON. Pp. 108. London: Kegan Paul, Trench, Trübner and Co. 1926. Price 2s. 6d.

Starting with the premise that speech is an intellectual function, that the neural arrangements underlying its activity constitute a physiological mechanism, and that the component units of the latter have an anatomical localization, the author discusses concisely but remarkably fully in the space at his disposal, speech and its derangements by disease from the anatomical, the physiological and the psychological standpoints. Each of these chapters of his book, as well as in that on the classification of aphasic disorders, bears the imprint of the author's intimate acquaintance with the conditions he describes. His attitude to the subject is based on this practical and personal experience, though he has been undoubtedly influenced by other writers, and especially by Hughlings Jackson and Bastian. He insists on the similarity of the cerebral functions in speech to those engaged in other higher activities, and that the scientific classification of aphasia must be physio-pathological.

There is no other book of its size which will prove so useful to the student in the study of the nature and the disorders of speech.

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